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(54) Title: INDUCTION OF IMMUNE TOLERANCE

(57) Abstract: Methods and compositions for the induction of immune tolerance in mammalian antigen presenting cells such as dendritic cells, macrophages, monocytes and B-lymphocytes are described. Such methods and compositions involve the use of agonists of the cell surface receptors CD36, CD51, thrombospondin receptors and/or the β-integrins which when exposed to an antigen-presenting cell such as a dendritic cell are able to inhibit maturation therein. Thus, the cells' ability to promote an immune response is inhibited. Tolerance to a specific antigen can be induced in antigen-presenting cells by exposure to one or more of the aforesaid agonists and the antigen. Thus, cell preparations can be prepared for administration to humans where tolerance to a specific antigen or antigens needs to be induced, for example in the case of allograft or xenograft transplants or in autoimmune disease.

INDUCTION OF IMMUNE TOLERANCE

The invention relates to the field of immune suppression and, in particular, to the identification of molecules which act as agonists of the cell surface receptors CD36, CD51 and thrombospondin receptors expressed on mammalian dendritic cells and other antigen-presenting cells, to *ex vivo* and *in vivo* uses of such molecules for inducing peripheral immune tolerance in mammals, to identification of molecules which inhibit the state of immune tolerance induced in a human by the binding of red blood cells infected with the malarial parasite to dendritic cells and to *in vivo* uses of such molecules in treating malaria.

Dysfunction of the immune system has been shown to play a role in the initial development and further progression of many human diseases. Impaired immune function can result in inability to fight infection or to destroy malignant cells as they develop within the body. Other diseases are caused because the immune system mounts an inappropriate response to a particular antigen. This inappropriate response might be to an external antigen resulting in atopic disease such as hay fever, asthma, eczema, coeliac disease and the like or to the body's own antigens resulting in auto-immune disease. For example both the non-organ specific auto-immune diseases, such as systemic lupus erythromatosis and rheumatoid arthritis and the organ specific auto-immune diseases such as auto-immune haemolytic anaemia and idiopathic thrombocytopenic purpura are associated with an inappropriate T-cell response to self-antigens.

Other auto-immune diseases where the antigen has been defined include auto-immune connective tissue syndromes, insulin dependent diabetes mellitus and auto-immune thyroid disease. Diseases where the antigen is less well defined include auto-immune skin

diseases such as eczema, psoriasis, alopecia areata and vitiligo, auto-immune diseases of the gastro-intestinal system such as inflammatory bowel disease and auto-immune hepatitis, auto-immune diseases of the nervous system such as multiple sclerosis and myasthenis gravis and auto-immune diseases of the kidney such as glomerulonephritis.

In view of the diseases associated with inappropriate immune response, particularly T-cell response, it is highly desirable to develop pharmaceuticals which are able to damp down certain of the body's immune defence mechanisms in order to alleviate the distressing symptoms associated with these diseases.

As well as treatment of diseases specifically associated with a mal-function of the immune system, down-modulation of immune mechanisms is desirable in circumstances where a recipient is exposed to allo-antigens or xeno-antigens for therapeutic purposes such as recipients of allogeneic or xenogeneic transplants. An allogeneic response in the case of allogeneic bone marrow transplantation or donor lymphocyte infusion might be avoided if one could induce a state of peripheral immune tolerance against donor cells in the recipient. Other examples of situations where down-modulation of immune mechanisms might be desirable include haemolytic disease of the new born, neo-natal allo immune thrombocytopenia or the therapeutic administration of antigenic substances such as blood products e.g. factor VIII, or any other therapeutic or prophylactic agent likely to induce an unwanted cellular immune response.

A cellular immune response is mediated by T-lymphocytes which are activated by antigen presenting cells, the most important of which are dendritic cells, which present antigen and activate memory T-cells and naive T-cells. Dendritic cells become

potent antigen-presenting cells when exposed to an immune stimulus and thereafter are described as "mature". Maturation confers enhanced ability to stimulate T-cells and a reduction in pinocytosis and phagocytosis compared with immature cells. Furthermore, maturation is accompanied by enhanced cell surface expression of HLA Class I and class II molecules as well as adhesion molecules, including CD54 and co-stimulatory molecules such as CD80, CD86 and the cell-surface marker CD83. Maturation of dendritic cells is also accompanied by the secretion of cytokines such as TNFα and IL12p70. The secreted cytokines have an autokrine effect on dendritic cell maturation itself and parakrine effects on interacting T-cells.

Immature dendritic cells present the cell surface antigens CD36 and CD51 (α_v) (part of the vibronectin receptor $\alpha_v\beta_3$). CD36 and integrin heterodimers $\alpha_v\beta_3$ or $\alpha_v\beta_5$ can be cross-linked by the soluble bridging molecule thrombospondin (TSP). Through studies of malarial infection the present inventors have discovered that dendritic cell maturation on exposure to an immune stimulus, for example, lipopolysaccharide (LPS), can be inhibited by molecules which bind to CD36 or to CD51 or both via the bridging molecule TSP and which act as agonists thereto.

This discovery is based on the inventors' initial observations that red blood cells infected with the material parasite *Plasmodium falciparum* adhere to dendritic cells via CD36 and/or TSP/CD51 (see Figure 1) and are able to inhibit the maturation thereof on exposure to LPS.

Plasmodium falciparum is one of the most successful human pathogens for which virulence factors remain poorly defined, although adhesion of infected erythrocytes to venular endothelium has been associated with some of the symptoms of severe

disease. Immune responses are unable to prevent symptomatic infections throughout life and immunity to severe disease develops only slowly during childhood. Understanding the obstacles to the development of protective immunity is crucial for rational approaches to prevent the disease.

Specific immunity to malaria has been attributed to cytotoxic lymphocytes active against the liver stage of infection or to antibodies reacting against blood stage antigens. Antigenic diversity, clonal antigenic variation and T-cell antagonism may contribute to evasion of the protective and parasiticidal host responses.

Furthermore, it is known that *Plasmodium falciparum*-infected erythrocytes adhere to endothelial cells and it has been widely assumed that this adhesion has evolved to mediate sequestration of parasites to endothelial cells in the peripheral tissues and so reduce their destruction by splenic macrophages.

The present inventors have now identified a further mechanism by which the malarial parasite prevents the infected host from mounting an effective immune response and preventing recurrence of the disease.

Specifically, the inventors have observed that human erythrocytes which are infected with *Plasmodium falciparum* are capable of adhering to human dendritic cells and that immature dendritic cells exposed to infected erythrocytes are no longer able to mature into full antigen-presenting cells or to stimulate T-cell proliferation, when subsequently exposed to an immune stimulus. However, this state of immune tolerance is not observed when the dendritic cells are exposed to uninfected erythrocytes, uninfected erythrocyte lysate, infected erythrocyte lysate, parasite-conditioned medium or a crude pigment

preparation derived from infected erythrocytes. Further, the effect is not observed when dendritic cells are exposed to erythrocytes infected with a *Plasmodium falciparum* strain T9/96 which is known not to be able to adhere to endothelial cells (Gardner et al (1996) Proc. Natl. Acad. Sci. USA 93 pp 3503-3508). This particular strain is not able to induce expression on the surface of infected erythrocytes of the parasite-derived protein pf-EMP-1 which is known to undergo clonal antigenic variation and is thought to be the mediator of adherence to endothelial cells. It has been reported that most parasite lines and clones adhere to the known cell-surface receptors CD36 and via TSP to CD51/61 ($\alpha_v\beta_3$). It is also known that pf-EMP-1 can bind to CD36. (see WO 96/33736).

The present inventors have now shown that CD36 and CD51 influence the process of dendritic cell maturation and that agonists thereof, including the malarial parasite derived protein pf-EMP-1, antibodies specific for CD36 and CD51, negatively charged phospholipids and apoptotic cells, are able to inhibit dendritic cell maturation in response to an immune stimulus. These agonists reduce the ability of the dendritic cells to stimulate T-cell proliferation in response to an antigen to a level which is lower than cells which have not been exposed to an immune stimulus at all. Thus, agonists of CD36 and CD51 can induce a state of immune tolerance.

It follows that agonists of CD36 and CD51 would be useful for the treatment of the types of autoimmune disease described above where an over-reaction of the host immune system is responsible for the symptoms. Further the inventors have found that dendritic cells may be treated by CD36 and/or CD51 agonists *in vitro* together with an antigen specific to the immune-response manifested in the auto-immune disease in question. Thus, tolerance may be induced to a

specific antigen so that, when the dendritic cells are reintroduced into the host, further auto-immune reaction is avoided or substantially reduced. In addition CD36 and CD51 agonists are useful for inducing a state of immune tolerance in both host and donor dendritic cells where bone marrow transplantation or lymphocyte infusion is contemplated. The feasibility of such treatment is demonstrated herein *in vivo* in mice. The ability to inhibit maturation of dendritic cells can be demonstrated *in vitro* so that molecules which act as CD36 or CD51 agonists can be easily identified in a high throughput screening assay.

As used herein the term "agonist" means a composition, molecule, cell or a component thereof which induces the same response when interacting with a receptor as the naturally-occurring ligand for that receptor.

In accordance with a first aspect the invention provides a method of identifying a molecule which is an agonist of cell surface receptor CD36 and/or CD51 as expressed by mammalian dendritic cells which method comprises:

a) exposing immature mammalian dendritic cells to the molecule to be tested,

b) exposing said immature dendritic cells to an immune stimulus and

c) determining the degree of maturation manifested by said dendritic cells,

wherein impaired maturation in response to the immune stimulus is an indication that said molecule under test is a CD36 and/or CD51 agonist.

Preferably, the method is performed using human

dendritic cells. As used herein the term dendritic cells means cells that present antigen to and activate lymphocytes and which are distinguished by their ability to activate, not only memory T-cells but also naive T-cells. Dendritic cells for use in the method of the invention may be derived by cultivation of adherent peripheral blood mononuclear cells with the addition of Granulocyte-Macrophage Stimulating Factor and Interleukin-4 for about 6 to 10 days. Such dendritic cells can be characterised by their level of expression of the cell-surface markers HLA Class I and II (high), CD11 c (high), CD3 and CD19 (negative), CD14 (low) and CD86 (high). These markers distinguish them from B-cells which are positive for CD19, T-cells which are positive for CD3 and macrophages which are CD14 high and CD86 low. (See Banchereau et al, (1998) Nature 392, 245-252). Antibodies to HLA Class I, HLA class II, CD14, CD3, CD19 and CD86 useful for identifying immature dendritic cells are commercially available as indicated in Table 1 below.

Dendritic cells which may be used in the method of the invention can also be derived directly from circulating peripheral blood mononuclear cells or by culture of CD34+ stem cells as described by Caux et al (1996) J. Exp. Med. 184:695-706 and Arrishi et al (1999) Blood 93:2244-2256.

There are various ways in which maturation of dendritic cells in response to an immune stimulus, may be measured. On maturation the dendritic cells become potent antigen presenting cells. As aforesaid maturation is accompanied by enhanced cell surface expression of HLA Class I and II molecules such as HLA DR, adhesion molecules such as CD54 and co-stimulatory molecules such as CD40, CD80, CD86 and CD83 which is a specific marker for mature dendritic cells. Thus, examination of the cell's antigen presenting ability, for example variety of antigens and/or level of

expression, is one way of determining whether maturation has occurred or whether it has been inhibited by the test molecule. Preferably, following immune stimulation, the level of expression of the HLA Class I and II molecules and/or adhesion molecules and/or co-stimulatory molecules is measured. In one embodiment maturation of dendritic cells is detected by measurement of the level of expression of two or more of the cell-surface antigens HLA DR, CD54, CD40, CD83 and CD86 whose level of expression is particularly enhanced. Preferably, the level of expression of all of the above in response to an immune stimulus is measured. Optionally the expression level of CD80 may also be measured.

Methods by which the expression of a cell-surface antigen may be quantified are well-known to those skilled in the art. The commonly used method is to apply an antibody specific for the antigen in question to the antigen-presenting cells which has been labelled to give a quantifiable detectable signal. Suitable labels are well-known to those skilled in the art and include radioactive labels, enzyme labels, fluorescent labels, metallic particles and the like. Antibodies suitable for carrying out the screening method of the present invention, as well as a commercial source, are shown in Table 1 below:

TABLE 1

Antigen	Antibody	Source
HLA DR	BF-1	Serotec
HAL Class 1	W32/6	ATCC HB-95
CD14	Tük4	DAKO
CD54	6.5B5	DAKO
CD40	LOB7/6	Serotec
CD80	BB1 or DAL 1	Serotec
CD83	HB15a	Serotec
CD86	BU63	Serotec
CD3	OKT3	ATCC CRL-8001
CD19	HD37	DAKO
CD36	clone 89	Serotec
	clone SMΦ	Immunocontakttec

Serotec: 22 Bankside, Station Approach, Kidlington, Oxford, UK DAKO Ltd: 16 Manor Courtyard, Hughenden Avenue, High Wycombe, Bucks HP13 5RE Immunokontakt: Centro Nord-Sud, CH-6934 Bioggio, Switzerland, Peprotec: 23 St. James Square, London SW9Y 4JH, UK, ATCC: 10801 University Boulevard, Manassas, VA 20110-2209; USA, Sigma: Sigma Alderich Company Ltd: Fancy Road, Poole, Dorset, BH12 4QH, UK, Schering-Plough: Schering-plough House, Shire Park, Welwyn Garden City, Herts, AL7 1TW.

As an alternative to measuring the level of cell surface antigen to determine whether or not dendritic cell maturation has occurred, it is possible to measure the cell's ability to induce T-cell proliferation. This is inhibited by agonists of CD36 or CD51. Dendritic cells which have been exposed to the molecule to be tested and to an immune stimulus

may be exposed to T-cells, for example allogeneic lymphocytes in a mixed lymphocyte reaction (MLR)with the T-cell receptor. The T-cells respond by growing and dividing, something which can easily be measured using methods well-known to one skilled in the art. For example, growth and division can be assessed visually using a light microscope to observe clumps of dividing cells. Alternatively, cell proliferation can be quantified using a suitably labelled metabolite, for example tritiated thymidine, which is incorporated into the cell's DNA.

A yet further alternative for determining the degree of dendritic cell maturation is to measure the level of secretion of cytokines such as TNFα, IL2p70 or IL10.

For example IL12p70 is secreted by mature cells but not by immature cells. The level of TNFα secretion is reduced in immature as opposed to mature cells. Kits are commercially available for detection and quantitation of all of the above cytokines. (see Examples). Preferably, the levels of TNFα, IL12p70 and IL10 secretion are measured.

In the screening method of the invention a variety of immune stimuli may be used. Suitable examples are lipopolysaccharide (available from Sigma), TNFα (available from Peprotec) and monocyte conditioned medium (MCM)the preparation of which is described by Romani et al (1996) J. Immunol. Methods, Sep 27; 196(2):137-51. Another suitable immune stimulant is CD40L which is expressed from plasmids having the ATCC Accession No's 79812,79813,79814 or 79815. The plasmids may be expressed in mouse fibroblasts STO (ATCC-CRL-1503).

It will be understood that TNFα would not be used as both immune stimulant and indicator of cell maturation in the same assay.

In a particular embodiment of the method of the

invention immature dendritic cells (about 10^6) are exposed in duplicate to various concentrations of the test molecule for about 3 to about 12 hours in a multiwell plate. The test compound is prepared in a suitable diluent which is not toxic to the dendritic cells such as tissue culture medium, PBS, water or a suitable non-toxic organic solvent, if appropriate. The duplicate wells are subsequently exposed to LPS (about 500 ng/ml) or left untreated for about 48 hours. For each concentration of the compound and time of exposure, the surface expression of the molecules identified above is compared with the surface expression on immature dendritic cells exposed to the test compound as well as untreated immature dendritic cells. The increase in cell surface expression is evaluated using indirect immunofluorescence and FACScan analysis. A compound is a candidate for further evaluation if the surface expression on dendritic cells of at least two cell-surface antigens is not increased by addition of the immune stimulant, LPS.

Preferably, molecules identified as potential CD36 or CD51 agonists by the method of the invention will be subject to further evaluation. For example, if surface expression of lineage-specific molecules has been used to determine the degree of maturation it would be usual to check whether the compound can also prevent immune-stimulated dendritic cells from inducing proliferation of T-cells and visa versa. The ability of the molecule to vary cytokine secretion could also be tested. In addition direct binding of the candidate molecule to CD36, CD51 or TPS should also be confirmed. This latter confirmation may be easily obtained by applying a sample of the candidate molecule to a purified sample of CD36, CD51 or TPS. Purified CD36 may be prepared as described by Tandon et al (1989) The Journal of Biological Chemistry, 264

pp 7570-7575. Purified CD51 may be prepared as described by Smith et al, (1990), Journal of Biological Chemistry, 265, 11008-11013 and purified TSP may be prepared as described by Silverstein et al (1985), Journal of Clinical Investigation, 75, pp 2065-2073.

Tests to detect binding of the test molecule are conveniently carried out by immobilizing the CD36, CD51 or TSP to a solid surface, for example the surface of a well of a microtitre plate. Methods of immobilization of protein molecules on such surfaces are well-known to those skilled in the art. The test molecule identified as a CD36 or CD51 agonist is then applied to the immobilized protein. Following removal of unbound test molecule the presence of bound molecule is directly detected. This may be achieved in a number of ways depending on the chemical or biochemical characteristics of the test molecule.

For example where the test molecule is a protein it would be usual to detect binding with a labelled antibody to that protein. If the test molecule is a non-antigenic small molecular weight compound then the compound itself may be radioactively labelled for detection.

The molecule whose activity is to be tested in the method of the invention may have any type of molecular structure. For example, it may be a protein, a peptide, an amino acid, DNA, RNA, PNA, a nucleotide or a nucleoside, or a low molecular weight compound. It may be a molecule having known pharmacological or biochemical activity or a molecule with no such known activity and may be a novel molecule. The method of the invention is suitable for testing entire libraries of molecules, for example libraries such as would be created by combinatorial chemistry. Indeed, all the embodiments of the screening method above may be adapted for an automated

high throughput compound screen.

Using the method of the invention the present inventors are able to confirm that the *Plasmodium falciparum* derived protein pf-EMP-1 is an agonist of both CD36 and CD51. In particular a fragment of pf-EMP-1 known as CIDR/A4 which comprises the CD36 binding domain is an agonist of CD36. CIDR/A4 is described by Smith et al (1998) Molecular and Biochemical Parasitology, 97, pp 133-148 and comprises amino acids 402 to 846 of pf-EMP-1 as shown in Figure 2.

Antibodies which bind CD36 and CD51 have also been identified as having agonist activity and are capable of inhibiting the maturation of dendritic cells. Thrombospondin is also an agonist of CD51. The present invention is also directed to any individual molecule identified as an agonist of CD36 or CD51 by the methods described herein.

The assays of the invention have allowed the inventors to make the further observation that apoptotic cells, the natural ligand of CD36, are also able to inhibit dendritic cell maturation in response to LPS. This is yet further evidence of the role of CD36 in modulating immune response.

In accordance with a second aspect the invention provides a pharmaceutical composition suitable for inducing immune tolerance in a mammal which comprises an agonist of the cell surface receptor CD36 and a pharmacologically acceptable carrier or diluent. The CD36 agonist may be a molecule identified by the method described above. Agonists which are suitable for incorporation into a pharmaceutical composition in accordance with the invention for the treatment of humans include antibodies with an affinity for an epitope of CD36, in particular an antibody which blocks the binding domain on CD36 for pf-EMP-1. Monoclonal antibodies specific for CD36 which are

designated "clone 89" and "clone SMΦ" and which are commercially available from Serotech or Immunocontact(details above) are suitable for use in the pharmaceutical compositions of the invention. Other commercially available CD36 antibodies which may be included in pharmaceutical compositions are listed in Appendix 1. It is contemplated that compositions comprising antibodies bispecific against CD36 and CD51 will be useful for inhibiting dendritic cell maturation.

Other agonists suitable for inclusion in pharmaceutical compositions are all variants of the *Plasmodum falciparium* pf-EMP-1 or fragments of such proteins which comprise the binding domain for CD36. A particular example is the fragment CIDR/A4 described herein comprising amino acids 402 to 846 of pf-EMP-1. (Figure 2).

Pharmaceutical compositions comprising a bispecific CD36 antibody and the CIDR/A4 fragment are also contemplated in accordance with the invention.

Yet another agonist suitable for inclusion in a pharmaceutical composition are negatively charged phospholipids such as phosphatidylserine containing liposomes which have also been shown to bind to CD36 and other cellular receptors of immune cells.

Yet another agonist suitable for inclusion in a pharmaceutical composition are apoptotic cells.

In a third of its aspects the invention provides a pharmaceutical composition suitable for inducing peripheral immune tolerance in a mammal which comprises an agonist of the cell surface receptor CD51 as expressed by mammalian dendritic cells and a pharmacologically acceptable carrier or diluent. As with CD36 acceptable agonists are antibodies, preferably monoclonal antibodies, directed against an epitope of CD51. Particularly suitable are antibodies blocking the binding domain of CD51 for the bridging

molecule TSP. Antibodies suitable for incorporation in a pharmaceutical composition in accordance with this aspect of the invention are commercially available and set out in Appendix 2.

Thrombospondin (TSP) is also suitable for incorporation into a pharmaceutical composition as a CD51 agonist. Preferably, such compositions also include the *Plasmodium falciparum* protein pf-EMP-1 or a fragment thereof incorporating the thrombospondin binding domain of pf-EMP-1.

As with CD36, negatively charged phospholipids such as phosphatidylserine are also suitable for incorporation as CD51 agonists in pharmaceutical compositions of the invention as well as apoptotic cells.

Pharmaceutical compositions in accordance with the second and third aspects of the invention are useful for the treatment of autoimmune diseases associated with inappropriate dendritic cell maturation and T-cell proliferation such as systemic lupus erythromatosis, rheumatoid arthritis, autoimmune haemolytic anaemia or idiopathic thrombocytopenic purpura. Vehicles suitable for delivery of pharmaceutically active substances are known to those skilled in the art, especially those for delivery of pharmaceutically active proteins.

In accordance with a fourth aspect of the invention there is provided a method of treating mammalian dendritic cells *in vitro* to induce immune tolerance therein which comprises exposing said cells to an agonist of cell surface receptors CD36 and/or CD51 as expressed on mammalian dendritic cells. The invention also relates to preparations of cells so treated. Suitable agonists are any of those agonists described above or any molecule or substance identified by the screening method described herein.

Treatment of dendritic cells *ex-vivo* with an

agonist of CD36 and/or CD51 is beneficial in many therapeutic applications as described hereinafter. For example, in the case of bone marrow transplantation or lymphocyte infusion recipient cells removed from the body are treated with agonists as described above to induce a state of immune tolerance therein. The treated cells are then re-introduced to the body before or simultaneously with the donor cells and the risk of allogeneic reaction is thereby reduced or eliminated. It is contemplated that dendritic cells of the donor may also be treated with a CD36 and/or CD51 agonist to induce immune tolerance. The donor may be allogeneic or xenogeneic.

The present inventors have demonstrated that in mice tolerance to foreign antigens can be achieved by exposure of dendritic cells from one mouse strain, *ex-vivo,* to a CD51 agonist followed by introduction of the treated cells into another strain of mice. Thus such therapy is expected to be applicable to humans.

In addition the present inventors have shown using a fragment of the α-subunit of the human acetylcholine receptor that immature dendritic cells treated with a CD36 agonist can be "modulated" to induce tolerance against a specific antigen by subsequent *ex-vivo* exposure to that antigen. Once reintroduced *in vivo*, immune response to that antigen is reduced or avoided. Thus, dendritic cells may be removed from a patient suffering from an auto-immune disease, for example, and exposed to a CD36 and/or CD51 agonist and an antigenic molecule associated with the auto-immune disease in question and the dendritic cell preparation, with or without maturation, reintroduced into the patient. Alternatively, this method may be used to induce tolerance to a particular allo or xeno-antigen or other therapeutic substance which is likely to induce an unwanted immune response,

such as a blood product like factor VIII.

Thus, the invention includes preparations of dendritic cells tailored to the treatment of a particular auto-immune disease by exposure to an agonist of CD36 and/or CD51 and the specific auto-antigen associated with the disease and cell preparations tolerant to other antigens likely to generate an unwanted immune response.

It follows from the inventor's observations concerning inhibition of maturation of dendritic cells with agonists of CD36 and CD51 that a similar effect will be observed with agonists of thrombospondin receptors in general and with other antigen-presenting cells of the immune system which also express CD36 and CD51 and thrombospondin receptors such as macrophages, B-lymphocytes and monocytes.

Thus, in accordance with a fifth aspect the invention provides a method of identifying a molecule which is an agonist of cell surface receptors CD36 and/or CD51 and/or a thrombospondin receptor as expressed on antigen-presenting cells of the mammalian immune system which method comprises:

a) exposing mammalian antigen-presenting cells to the molecule to be tested,

b) exposing said cells to an immune stimulus and

c) determining the response to said immune stimulus by said cells,

wherein an impaired response compared to the response in the absence of said test molecule is an indication that said molecule under test is a CD36 and/or CD51 agonist or an agonist of a thrombospondin receptor.

Preferably, the response that is measured is maturation of said antigen presenting cell. Such a

screening method may be carried out using the general methodology already described herein for dendritic cells. For example, monocytes can be purified from peripheral blood by adherence of PBMC to plastic dishes. Non-adherent cells are removed and the adherent cells can be detached by incubation with EDTA in PBS. Contaminating lymphocytes are depleted with the aid of magnetic heads and antiCD3 and antiCD19 monoclonal antibodies. Macrophages may be generated by culturing monocytes, which have been isolated as described above, in RPMI 1640 supplemented with M-CSF for six days. β-lyphocytes can be isolated from blood by virtue of their non-adherence to plastic petri dishes. The non-adherent cells are subjected to depletion of contaminating monocytes and T-cells by exposure to magnetic heads and antiCD14 and antiCD3 monoclonal antibodies.

Once isolated the antigen presenting cells are exposed to a substance to be tested for agonist activity against CD36, CD51 or a thrombospondin receptor and the degree of activation of said cells is measured. As with dendritic cells, activation may be determined by measuring the levels of secretion of various cytokines, or by testing ability of said antigen presenting cells to stimulate T-cell proliferation. In a preferred embodiment the increased expression of certain cell surface receptors is used as a measure of activation. In the case of monocytes and macrophages activation is accompanied by an increase in surface expression of HLA-DR, CD54 and CD86 which is measured in the manner described above, preferably with the use of a monoclonal antibodies to HLA-DR, CD54 and CD86. B-cell activation is determined by measuring the level of cell surface expression of HLA-DR, CD86 and CD40. The expression may be detected using antibodies to these cell surface receptors. Such as clone BF1, Serotech (HLA DR) clone

BU63, Serotech (CD86) and clone TRAP1 (Pharmingen) (CD40).

The invention also further relates to uses of an agonist as identified above using said antigen-presenting cells for treatment of any of the auto-immune diseases listed above and for inducing immune tolerance in said antigen presenting cells *ex-vivo* as well as to antigen-presenting cell preparations which have been treated with a CD36 and/or CD51 agonist and/or thrombospondin receptor agonist and optionally an antigenic material.

The invention also relates to pharmaceutical compositions comprising an agonist of a thrombospondin receptor, for example $\alpha_v\beta_3$ or $\alpha_v\beta_5$, with a pharmaceutically acceptable carrier or diluent suitable agonists include antibodies to the thrombospondin binding domain of said receptor, for example any of the antibodies listed in Appendix 3.

Other suitable agonists include negatively charged phospholipids such as phosphatidylserine containing liposomes.

It is a further conclusion from the work of the present inventors that agonists of β-integrin associated with the cell surface receptor CD51 as expressed on the surface of antigen-presenting cells of the mammalian immune system, will also be useful for inducing immune tolerance. The invention in a sixth aspect thus, further relates to methods of identifying β-integrin agonists by any of the procedures described above and to uses of β-integrin agonists, as defined above, for any of the medical uses which are described herein.

In a seventh aspect the present invention further relates to uses of apoptotic cells as a medicament for inducing immune tolerance in antigen-presenting cells, preferably dendritic cells and to pharmaceutical compositions comprising those cells in a suitable

carrier or diluent. Apoptotic cells are suitable for delivering tissue specific antigens including major and minor histocompatibility antigens to dendritic or other antigen-presenting cells. Delivering antigens in this way allows delivery of unknown antigens or antigens where the class II restricted epitope(s) are not defined. The tissue origin of the apoptotic cell may be varied depending upon the application. For example, it is preferred for the apoptotic cell to be of the same tissue type as any cell bearing an antigen to which tolerance is to be induced.

In accordance with an eighth aspect the invention further relates to the use of negatively charged phospholipids for inducing immune tolerance in antigen presenting cells. Said immune tolerance may be induced by treatment of said antigen presenting cells, for example dendritic cells, with said negatively-charged phospholipid either *ex-vivo* by the methods described herein or by administration of the phospholipid to a patient by any of the conventional administration routes known to those skilled in the art. A preferred form of composition is liposomes comprising the negatively charged phospholipid. A preferred phospholipid is phosphatidylserine.

Since the inventions of the present application were developed following the basic observation that *Plasmodium falciparum* infected erythrocytes adhere to dendritic cells and inhibit the maturation thereof it follows that molecules which block or inhibit such adherence may be useful as pharmaceuticals in the clinical management of malaria, in particular molecules which inhibit adherence of parasite-infected erythrocytes to CD36 or TSP.

Thus, in accordance with a ninth aspect of the invention a method comprising the following steps is used to identify a molecule capable of preventing adherence of erythrocytes infected with a malarial

parasite to human dendritic cells:

(a) exposing a purified preparation of CD36 or TSP to:-

(i) the molecule to be tested and

(ii) parasitsed human erythrocytes

either consecutively or simultaneously and

(b) determining the level of adherence of said parasitised erythrocytes to said CD36 or TSP

wherein a reduction in the level of adherence to CD36 or TSP in the presence of the test molecule compared to the level of adherence in the absence of said test molecule is an indication that said molecule is capable of preventing the adherence of erythrocytes infected with the malarial parasite to human dendritic cells.

The erythrocytes may be infected with *Plasmodium falciparum* or another Plasmodium species. Suitable *falciparum* strains include ITO/A4 or ITO/C24 which may be derived as described by Roberts et al (1992) Nature 357 pp 689-692 or Malayan Camp (MC) which may be obtained as described by Roberts et al (1985) Nature 318:64-66.

A suitable format for carrying out a screening method as described above is to immobilize the purified CD36 or TSP onto a solid surface. Preferably, immobilization is secured by adsorption of the protein molecules to a plastic surface such as a petri dish. Parasitised erythrocytes suspended in a suitable binding medium are added to the adsorbed CD36 or TSP and incubated for a period sufficient to allow adherence, for example, about 1 hour. Thereafter the binding medium and any non-adhered erythrocytes are removed and a suitable erythrocyte stain for example, Giemsa, added to the petri dish. Adhered erythrocytes

may be quantified by counting under a light microscope. Alternatively, depending on the stain used, erythrocyte adherence may be quantified by spectrometry, fluorescence microcopy and the like.

In a tenth aspect the invention provides a method of identifying a molecule capable of preventing the adherence of red blood cells infected with a malarial parasite to human dendritic cells which comprises:

a) exposing immature human dendritic cells to the *Plasmodium falciparum* protein pf-EMP-1 or an active binding domain thereof in the presence or absence of the molecule to be tested,

b) exposing said immature dendritic cells to an immune stimulus and

c) determining the degree of maturation manifested by said dendritic cells,

wherein any maturation of said dendritic cells in the presence of the test molecule over and above that manifested in the absence of said molecule is an indication that said molecule is capable of preventing adherence of red blood cells infected with a malarial parasite to human dendritic cells.

Maturation of dendritic cells may be measured by any of the methods already described herein. Suitable immune stimulants include LPS, TNFα, CD40L and monocyte conditioned medium (MCM). Preferably the pf-EMP-1 preparation for use in the method is that designated in pf-EMP-1 A4var as described by Smith et al (see before) and having the Genbank Accession No. L42244. The fragment CIDR/A4 may also be used.

In a further aspect the invention provides for use of molecules identified by the aforementioned methods which inhibit infected erythrocyte adherence

to dendritic cells in pharmaceutical compositions for the treatment of malarial infection.

Based on the present inventors' observations it is further contemplated that a modified CIDR region of the pf-EMP-1 A4 variant protein could be incorporated in a multisubunit vaccine against *falciparum* malaria. This would induce blocking antibodies against the CD36 binding domain of pf-EMP-1 variant proteins so that the immune responses against other proteins are not inhibited.

All documents cited in this application are incorporated herein by reference.

The invention will now be further described with reference to the following Figures and Examples.

FIGURE 1 shows schematically the molecular basis for the binding of Plasmodium falciparum infected red blood cells to CD36 and TSP on the surface of dendritic cells;

FIGURE 2 shows the amino acid sequence of the pf-EMP-1 fragment CIDR/A4;

FIGURE 3 shows the increase in surface expression of dendritic cell marker antigens HLA DR, CD54, CD40, CD80, CD83 and CD86 following immune stimulation after exposure to (a) LPS matured dendritic cells, (b) dendritic cells matured with LPS, with and without prior exposure to RBC, (c) dendritic cells matured with LPS with and without prior exposure to parasite lysate and (d) dendritic cells matured with LPS with and without prior exposure to intact ITO/A4 infected RBC;

FIGURE 4; (A) shows the absolute binding of erythrocytes infected with parasite lines ITO/A4, ITO/C24, MC and T9/96 to CD54, CD56, and TSP (a,c,e,g)

and (B) shows the increase in surface expression of LPS matured dendritic cells compared with dendritic cells exposed to the respective parasite line prior to maturation (b,d,f,h);

FIGURE 5 shows transmission electron micrographs illustrating the interaction of dendritic cells with (a) ITO/A4 infected erythrocytes and (d) non-adherent T9/96 infected erythrocytes;

FIGURE 6 shows dendritic cell stimulation of T-cell proliferation (a) induced by immature dendritic cells (■), LPS-matured dendritic cells (□) and dendritic cells co-cultivated with intact ITO/A4 infected erythrocytes (▼) prior to maturation, primary CD4+ T-cell responses to parasite lysate (b) and to keyhole limpit haemocyanin (c) induced by LPS-matured autologous dendritic cells (□,○) and autologous dendritic cells co-cultivated with intact ITO/A4 infected erythrocytes (■,●)prior to maturation;

FIGURE 7 shows the effect of monoclonal antibodies against CD36 and CD51 on maturation of dendritic cells represented graphically as relative increase in surface expression of dendritic cells matured with LPS compared with immature dendritic cells;

FIGURE 8 shows the effect of monoclonal antibodies against CD36 and CD51 on dendritic cell maturation as a FACscan output;

FIGURE 9 shows further results of experiments with apoptotic cells (a) output of FACscan,(b) staining with potassium iodide to exclude dead cells, (c) proliferation of allogenic T-cells stimulated by increasing numbers of immature dendritic cells,(◆)LPS-matured dendritic cells (▲) or dendritic cells

exposed to apoptotic dendritic cells and then matured with LPS(■).

FIGURE 10 shows the effect of apoptotic neutrophils on the maturation of dendritic cells;

FIGURE 11 shows results of a T-cell proliferation assay including antigen specific T-cell proliferation. (a) Proliferation of allogeneic T-cells. (b) proliferation of KLH specific CD4+CD45RO- autologous T-cells (c, d) proliferation of the T-cell clone TB-2 specific for the human Acetylcholine Receptor a-subunit in response to polypeptide (c) or peptide (d). Stimulator dendritic cells were treated as follows: immature DC alone (x) or matured with LPS (□); dendritic cells exposed to irrelevant antibodies with (O) or without (●) antigen and then matured with LPS; dendritic cells exposed to antiCD36 antibody with (▽) or without (▼) antigen and then matured with LPS; dendritic cells exposed to antiCD51 antibody with (△) or without (▲)antigen and then matured with LPS; dendritic cells exposed to antiCD36 and antiCD51 antibody with (◇) or without (◆) antigen and then matured with LPS.

FIGURE 12 shows secretion of cytokines TNFα, IL12p70 and IL10 by dendritic cells exposed to an antiCD36 antibody or to apoptotic dendritic cells and respective controls;

FIGURE 13 shows *in vitro* maturation of mouse dendritic cells following exposure to an antiCD51 antibody; and

FIGURE 14 shows results from mouse popliteal lymph node assay.

EXAMPLE 1

Generation of antigen-presenting cells

(a) Dendritic cells

Immature dendritic cells were derived from peripheral human blood cells using standard procedures as described by Sallusto et al (1995) J. Exp. Med. 182 pp 389-400. Briefly, monocytes were cultivated in RPMI 1640 supplemented with 2mM Glutamine, 50 µg/ml Kanamycin, 1% nonessential amino acids (GibcoBRL), 10% human AB serum and 50 ng/ml of each IL-4 (specific activity >$2x10^6$ U/mg, PeproTech) and GM-CSF (specific activity > $1x10^7$ U/mg, Schering-Plough) for 6 days. Between day six and day nine of the culture non-adherent immature dendritic cells were harvested and purified by depletion of contaminating lymphocytes with the aid of magnetic beads (Dynal) and anti-CD3 and anti-CD19 monoclonal antibodies (DAKO).

(b) Monocytes

Monocytes were purified from peripheral blood by adherence of PBMC to plastic dishes for 2 hours. Non adherent cells were removed and the adherent cells layer washed 2 times with warm PBS. For further purification, the adherent cells were detached by incubation with 2 mM EDTA in PBS for 20 min and contaminating lymphocytes depleted with the aid of magnetic beads (Dynal or Miltenyi) and anti-CD3 and anti-CD19 monoclonal antibodies (DAKO).

(c) Macrophages

Monocytes isolated as described above were cultured in RPMI 1640 supplemented with 2 mM Glutamine, 50 µg/ ml Kanamycin, 10% human AB serum and 50 ng/ml of M-CSF (specific activity > 2 x 10^6 U/mg, Peprotech) for 6

days.

(d) B-lymphocytes

B-lymphocytes were isolated from human blood according to standard procedures. Briefly, non-adherent PBMC were subjected to depletion of contaminating monocytes and T-cells with the aid of magnetic beads (Dynal or Miltenyi) and anti-CD14 and anti-CD3 monoclonal antibodies (DAKO). B-cells were cultured in RPMI 1640 supplemented with 2 mM Glutamine, 50 µg/ ml Kanamycin, 1% to 10% human AB serum.

(e) CD34+ Cells

CD34+ cells were isolated from PBMC with the aid of anti-CD34 antibody conjugated magnetic beads (Dynal or Miltenyi). CD34+ progenitor were then cultured in RPMI 1640 supplemented with 2 mM Glutamine, 50 µg/ ml Kanamycin, 1% to 10% human AB serum and the following cytokines: 100 ng/ml of GM-CSF (Schering-Plough), 50 ng/ml TNFα and 50 ng/ml SCF (Peprotech) for 12 days. As an alternative, CD34+ cells could be expanded in the above mentioned medium but supplemented with 25 ng/ml FLT3-L , 10U/ml TPO, SCF 20 ng/ml (Peprotech) for up to 8 weeks and then induced to differentiate to dendritic cell by culture of a further 3 days in medium supplemented with 25 ng/ml GM-CSF and 25 ng/ml IL-4."

EXAMPLE 2

Maturation assay

(a) For maturation assays $1x10^6$ purified dendritic cells were incubated in duplicate wells (a) with

100 ng/ml LPS, (b) with 100ng/ml LPS with or without prior exposure to $1x10^8$ RBC, (c) with 100 ng/ml LPS with or without prior exposure to parasite lysate corresponding to $1x10^8$ parasite infected RBC, (d) 100 ng/ml LPS with or without prior exposure to $1x10^8$ intact ITO/A4 infected RBCs. Incubation with LPS (Salmonella typhimurium) was for a period of 48 hours.

Maturation of the dendritic cells was measured using monoclonal antibodies to the following human cell surface markers: CD3 clone OKT3, HLA A,B,C clone W32/6, CD14 clone Tuk4, CD54 clone 6.5B5, CD19 clone HD37 (DAKO): CD36 clone 89 (IgG1) or clone SMQ(IgM), CD80 clone BB1, CD40 clone LOB7/6, CD86 clone BU63, HLA DR clone BF-1 (Serotec), CD83 clone HB15a (Zhou et al (1995) J. Imm. 154, pp3821-3835. Staining of dendritic cells was performed as described by Zhou et al above and immunofluorescence analysed by FACScan (Becton Dickenson). All experiments were repeated at least six times with dendritic cells obtained from different donors. Dead cells were excluded from analysis using Propidium Iodide. The results are shown on Figure 3. The relative increase of surface expression is expressed as the mean fluorescence intensity (MFI) of matured dendritic cells over the MFI on immature dendritic cells.

The results show that dendritic cell maturation is inhibited by the direct interaction with intact infected erythrocytes and is not due to the secretion of inhibitory parasite products or a toxic effect of parasite debris.

The differences in surface expression on dendritic cells exposed to intact infected erythrocytes to dendritic cells alone are statistically significant for all markers with $p<0.01$ (Student t-test).

(b) Other antigen-presenting cells

For maturation assays 1 x 10^6 purified monocytes or macrophages were incubated in duplicate wells with or without LPS in the presence of medium alone, antibodies such as anti-CD36 or anti-CD51 or control antibodies, apoptotic cells or necrotic cells. Maturation was measured by the increase in surface expression of HLA-DR, CD54 and CD86 using the antibodies and flow cytometry as described above.

For maturation assays 1 x 10^6 purified B-cells were incubated in duplicate wells with or without LPS in the presence of medium alone, antibodies such as anti-CD36 or anti CD51 or control antibodies, apoptotic cells or necrotic cells. Activation was measured by the increase in surface expression of HLA DR (clone BF-1, Serotec), CD86 (clone BU63, Serotec) and CD40-Ligand (clone TRAP1, Pharmingen) and flow cytometry.

EXAMPLE 3

Cultivation of Plasmodium falciparum infected red blood cells

Laboratory strains of Plasmodium falciparum were cultured in human RBC as described by Trager et al (1976) Science. 193 pp673 to 675. The cytoadherent cell lines ITO/A4 and ITO/C24 were clones isolated by manipulation from the ITO4 line, which is derived from a parasite isolate from Ituxi in Brazil. The cytoadherent parasite line Malayan Camp (MC) and the non-adherent cell line T9/96 were both adapted to in vitro culture from parasites originally isolated from Thailand.. All cultures were free from mycoplasma contamination. Infected erythrocytes were purified

either by differential sedimentation in Plasmagel or through 65% Percoll both of which gave a yield of more than 90% infected erythrocytes. Examination of a thin film revealed that more than 90% of infected erythrocyes were viable. Parasite lysate was obtained by three rounds of freezing and thawing of mature infected RBC. Parasite pigment was prepared as described by Schwarzer et al (1994) BR. J. Haematol. 88, pp740-745. Parasite conditioned medium was the supernatant derived after culturing $1x10^8$ purified infected erythrocytes in dendritic cell medium for 24 hours. All materials were from Sigma unless otherwise stated.

EXAMPLE 4

Binding of parasites to purified proteins

Binding of parasitised RBCs to purified proteins was measured as previously described by Craig et al (1997) Infect. Immun. 65, pp 4580-4585. Briefly, two microlitres of a solution of TSP (Gibco-BRL), purified CD36 or purified CD54 (ICAM-Fc) were adsorbed onto bacteriological, plastic plates. Mature erythrocytes parasitised with P. falciparum strains (a) ITO/A4, (c) ITO/C24, (e) MC and (g) T9/96, were suspended in binding medium and added to each dish. The erythrocytes were allowed to settle and then resuspended by gentle rotation every 10 minutes for 1 hour. Non-adherent cells were removed, the remaining cells fixed and stained with Giemsa. Adherent parasitised cells were counted by light microscopy and the number of cells bound per square millimeter were corrected to binding at 2% haematocrit and 5% parasitaemia. The results are shown in Figure 4A and confirm that like ITO/A4, ITO/C24 and MC are able to

adhere to CD36 and TSP. However, their adherence to CD54 was much reduced. T6/96 does not adhere to CD54, CD36 or TSP.

EXAMPLE 5

Effect of parasite strains on maturation

A maturation assay as described in Example 2 was carried out but exposing immature dendritic cells to erythrocytes infected with (b) ITO/A4, (d) ITO/C24, (f) MC and (h) T9/96. The results are shown in Figure 4B. While parasite lines MC and ITO/C24 inhibited the maturation of dendritic cells in a similar vein to clone ITO/A4, the non-adherent line T9/96 did not inhibit maturation of dendritic cells even at a ratio of infected erythrocytes to dendritic cells of 100:1.

EXAMPLE 6

Electron microscopy

Adherence of ITO/A4 infected erythrocytes but not T9/96 infected erythrocytes to dendritic cells was confirmed by electron microscopy. One million purified immature dendritic cells were incubated for 2 hours and for 12 hours with $1x10^8$ ITO/A4 infected RBC (a) or T9/96 infected (d) in 2 ml of dendritic cell medium , harvested and fixed with 2.5% glutaraldehyde/cacodylate buffer. Cells were post fixed in osmium tetroxide, dehydrated and embedded in epoxy resin. Thin sections were stained with uranyl acetate and lead citrate prior to examination in a Joel 1200EX electron microscope. The number of adherent and infected erythrocytes and the number of phagosomes containing pigment granules was counted in

each sample in thin sections of 100 randomly selected dendritic cells. Transmission electron micrographs are shown in Figure 5.

Note the cell processes partially enclosing infected erythrocytes (arrows in a) and the close apposition of the limiting membranes of the infected erythrocytes and dendritic cells particularly at the knobs (b, arrowhead). Within dendritic cell cytoplasm are phagosomes containing characteristic pigment granules (c, arrows). N -dendritic cell nucleus, P - infected erythrocyte. Bars are 2 μm (a and d), 200 μm (b), 500 μm (c).

ITO/A4 infected erythrocytes were observed to be in intimate contact with immature dendritic cells with cytoplasmic processes partially enclosing the parasites (Fig. 5a). The plasmalemma of the infected erythrocytes was in close apposition to the limiting membrane of the dendritic cell particularly at the site of knobs (Fig. 5b). A similar apposition between parasitised erythrocytes and host cells is seen between infected red blood cells and endothelial cells (Berendt et al (1994) Parasitology 108 Suppl. 519-28). In contrast, only a few infected erythrocytes of the T9/96 strain were associated with the dendritic cells (Fig. 5d). When quantified, ten times more ITO/A4 infected erythrocytes were found adherent to dendritic cells than T9/96 infected erythrocytes in 100 thin sections of dendritic cells. Furthermore, ingestion of intact ITO/A4 infected erythrocytes by dendritic cells was not observed during this time. Nevertheless, phagocytosis of parasite debris as revealed by the number of phagosomes containing pigment granules (Fig. 5c) was similar for dendritic cells incubated with ITO/A4 or with T9/96.

EXAMPLE 7

T-cell proliferation assays

Total-T-cells (allogeneic MLR) or CD4+ T cells (primary T-cell responses) were purified using a Cellect column (TCS). For the allogeneic MLR, dendritic cells were added in increasing numbers (156 to 10,000) to 1 x 10^5 T-cells in triplicate and incubated for 5 days. T-cells were pulsed with 0.5 µCi 3H-thymidine/well for the last 18 hours of the culture. For primary T-cell responses, 1 x 10^6 dendritic cells were incubated with medium alone or with 1 x 10^8 infected erythrocytes for 18 h and then pulsed with 10 µg/ml parasite-lysate or with 30 µg/ml keyhole limpet haemocyanin, respectively. The dendritic cells were purified by sedimentation through Lymphoprep™ and 1 X 10^5 dendritic cells were culterd with 1.5 x 10^6 CD4+ T-cells from the same donor. From day 4 to day 6 of culture, 50 µl aliquots were taken in triplicate and pulsed with 0.5 µCi ^{3}H-thymidine/well for 8 hours.
(see Plebanski et al (1992) Immunol. 75 86-90). The results are shown in Figure 6.

Dendritic cells exposed to intact infected erythrocytes are poor stimulators of T-cell proliferation. Allogeneic T-cell proliferation (a) induced by immature dendritic cells (■), LPS-matured dendritic cells (□) and dendritic cells co-cultivated with intact ITO/A4 infected erythrocytes (▼) prior to maturation. Primary CD4+ T-cell responses to parasite-lysate (b) and to keyhole limpet haemocyanin (c) induced by LPS-matured autologous dendritic cells (□,○) and autologous dendritic cells co-cultivated with intact ITO/A4 infected erythrocytes (■,●) prior

to maturation. Data from one out of three independent experiments are shown.

Dendritic cells matured after incubation with uninfected RBC, a crude pigment preparation or a lysate of infected erythrocytes induced a similar degree of T-cell proliferation in a mixed leukocyte, reaction to that induced by control mature dendritic cells (data not shown).

However, dendritic cells incubated with LPS after exposure to intact infected erythrocytes from the parasite line ITO/A4 were strikingly less efficient in their induction of T-cell proliferation compared with the T-cell proliferation induced by mature dendritic cells (Fig 6a). Furthermore, dendritic cells exposed to intact infected erythrocytes before maturation with LPS did not induce primary CD4+ T-cell responses to lysate of infected erythrocytes or to keyhole limpet haemocyanin (Plebanski et al) (Fig 6, b,c).

It is concluded that the maturation of dendritic cells and their subsequent ability to activate T-cells is profoundly inhibited by their interaction with intact infected erythrocytes. Non-adherent parasite lines, parasite debris and crude pigment do not modulate dendritic cell function in this way. These studies provide one explanation for the clinical and experimental evidence of immune dysregulation during malaria infection such as the impairment of the delayed-type hypersensitivity response to recall antigens and the antibody response to vaccines.

EXAMPLE 8

Maturation assay with monoclonal antibody

A maturation assay was carried out as described in Example 2 except that instead of infected erythrocytes the immature dendritic cells were exposed to monoclonal antibodies to CD36, CD51 or both prior to immune stimulation with LPS. Specifically, $1x10^6$ purified dendritic cells were incubated in duplicate wells without or with either 25 µg irrelevant IgM antibody, 25 µg irrelevant IgG1 antibody, 25 µg antiCD36 antibody, 25 µg antiCD51 antibody or a combination thereof for at least 3 hours. Thereafter, dendritic cells were matured with 100 ng/ml LPS (*Salmonella typhimurium*) for 48 hours or left untreated as a control. The monodonal antibodies tested were CD36 clone SMQ (Immunocontact) and clone 89 (Serotec), CD51 clone 13C2 (Immunocontact), IgM isotope control clone MOPC, IgG isotope control clone MOPC (Sigma). The results of two experiments are shown in Figures 7 and 8 respectively. As will be apparent both CD36 and CD51 antibodies have the effect of inhibiting dendritic cell maturation in a similar manner to infected erythrocytes.

EXAMPLE 9

Maturation assay with apoptotic cells

A maturation assay was carried out as described in Example 2 except that instead of infected erythrocytes the immature dendritic cells were exposed to apoptotic cells prior to immune stimulation with LPS. Apoptotic or necrotic cells were derived from purified autologous dendritic cells, monocytes or neutrophils. Specifically for maturation assays in the presence of apoptotic bodies $1x10^6$ purified dendritic cells were incubated in

duplicate wells without or with either 2 x 10^6 autologous apoptotic or necrotic cells for 12 hours. Maturation was induced by the addition of LPS or TNFα as stated above. Apoptosis was induced by radiation with a calibrated UV lamp at a dose of 2500 mJ/cm^2 and evaluated by staining with FITC-AnnexinV/Propidium Iodide according to manufacturers recommendations (Roche Diagnostics) 3 hours and 12 hours after UV radiation. Necrosis was induced by at least three cycles of rapid freezing at -70°C and thawing at 37°C. Thereafter, more then 90% of cells were permeable for trypan blue. The results are shown in Figure 9 as follows:

Apoptotic cells but not necrotic cells inhibit the maturation of dendritic cells. (a) Immature dendritic cells were left untreated, matured with LPS or exposed autologous apoptotic or necrotic dendritic cells prior to maturation with LPS and subsequently stained with antibodies directed against surface marker and analysed by FACScan as indicated. (b) Dead Cells and especially apoptotic cells were efficiently excluded from analysis by gating on forward scatter and exclusion of cells positive for Propidium Iodide. (c) Proliferation of allogeneic T-cells stimulated by increasing numbers of immature dendritic cells (◆), LPS-matured cells (▲) or dendritic cells exposed to apopotic dendritic cells and matured with LPS (■).

The results of a further experiment with apoptotic neutrophils shown in Figure 10.

EXAMPLE 10

Antigen specific T-cell responses

The proliferative response of the CD4+ T-cell clone

TB-2 for the peptide 144-163 of the human acetylcholine receptor (Nagvekar N et al, J. Clin in est, 1998 101 (10) pp 2268-77) was analysed. T-cell proliferation was measured as described in Example 7. For antigen-specific T-cell responses, 1 x 10^6 dendritic cells were incubated with medium alone or with antibodies as indicated and then pulsed for 6 h with 0.025 mM AChR α: 3-181 polypeptide before or 1 mM AChR α:144-163 peptide after maturation with LPS. For antigen specific T-cell responses of the clone TB-2 increasing numbers of MHC class II matched dendritic cells were incubated with 3 x 10^4 T-cells for 72 h. Proliferation was measured in all assays by adding 0.5 mCi ^{3}H-thymidine/well for the last 8 hours of the culture.

The results are shown in Figure 11 (c) and (d). Exposure of dendritic cells to antiCD36, antiCD51 or both antibodies abolished their ability to induce proliferation in the T-cell clone as compared to dendritic cells exposed to irrelevant antibodies (Fig 2c, d). The proliferation of the T-cell clone remained low even when the modulated dendritic cells were exogenously loaded with peptide thus excluding a defect in antigen-uptake or antigen-processing due to the presence of antibodies.

EXAMPLE 11

Cytokine production by dendritic cells

Secretion of the cytokines TNF alpha, IL12 p70 and IL10 was measured in supernatants of dendritic cells treated with either anti-CD36 antibody or apoptotic cells or in the respective controls before or after maturation with LPS for 24 hours using commercially

available ELISA kits. These kits can be obtained from R and D Systems, Europe Ltd. 4-10, The Quadrant, Barton Lane, Abingdon, Oxford, OX143 YS and BD Pharmingen, 10975, Torreyana Road, San Diego, CA 92121, USA.

Maturation with LPS induced secretion of TNF-α by dendritic cells irrespective whether they were exposed to anti-CD36 antibodies or apoptotic cells although the concentration of TNF-α was consistently slightly lower than in the respective controls. IL12 p70 was secreted by control dendritic cells matured with LPS whereas IL10 was secreted by dendritic cells exposed to anti-CD36 antibodies or apoptotic cells. Of note, the absolute amount of IL10 varied considerably between dendritic cells treated with anti-CD36 and dendritic cells exposed to apoptotic cells in response to LPS. It is possible that intact cells bind to more than one receptor thus modifying the cytokine secretion induced by CD36 alone. However, we investigated whether secretion of IL10 had a role in inhibition of dendritic cell maturation due to ligation of CD36 by maturing dendritic cells exposed anti-CD36 antibodies or to apoptotic cells in the presence of blocking anti-IL10 antibodies. The inhibition of dendritic cell maturation was not reversed (data not shown) and is therefore independent of the secretion of IL10.

EXAMPLE 12

Modulation of mouse dendritic cell maturation and function by antiCD51 antibodies *in vitro* and *in vivo*

Rationale

Since human monocyte derived dendritic cells can be modulated in their maturation and function by a variety

of agents including antibodies binding to CD36 and or CD51, in this study we began to investigate whether a similar phenomenon could be observed in mouse dendritic cells.

Methods

Generation of bone-marrow derived dendritic cells: Bone marrow from male Balb/c (H-2^k) mice was harvested and total cells were cultured in RPMI supplemented with 2 mM glutamine, 50 mg Kanamycin, 10 % FCS,10 ng/ml each murine recombinant GM-CSF and IL-4. On day two of culture half the medium was replaced with fresh medium supplemented with cytokines and on day four of culture non-adherent cells were harvested.

In vitro maturation of bone-marrow derived mouse dendritic cells: One million of bone marrow derived dendritic cells (approximately 50% total cells) in duplicate were exposed to either medium alone, 25 mg isotpype control antibody or 25 mg antiCD51 antibody for 8 hours. Cells were subsequently exposed to 100 ng LPS for 48 hours or left alone as a control. Maturation of dendritic cells was analysed by double staining with FITC conjugated antibodies against CD11c and PE-conjugated antibodies directed against either CD40, CD54, CD86 or I-A and subsequent FACScan analysis. Analysis was performed on CD11c-FITC positive cells.

Popliteal lymph node assay: Dendritic cells were exposed to medium alone or to antiCD51 antibodies and then matured with LPS as described above. The cells were then harvested and washed four times in PBS in order to remove LPS. Cells were resuspended in 10% FCS/PBS at a concentration of 6 x 10^5 total cells/20 ml. Groups of six male C3H3/HE (H-2^d) mice were injected with 20 ml of PBS into the right footpad and LPS matured dendric cells into the left footpad, with 20 ml

of PBS into the right footpath and dendritic cells exposed to antiCD51 antibody prior to LPS maturation into the left footpad or with 20 ml of PBS into the right and the left footpad. After one week mice were sacrificed and the popliteal lymphnodes were removed. The weight of the left and the right lymphnode of each mouse in all three groups were determined and the ratio of the weight of the left lymphnode to the weight of the right lymphnode was calculated. The mean and SE of the ratio was determined for each group.

Results

Dendritic cells matured with LPS (DC LPS) increased the surface expression of the molecules CD40, CD54 and CD86 as compared to immature dendritic cells (DC). However, when dendritic cells were treated with antiCD51 antibodies prior to exposure to LPS (DC CD51 lps), the dendritic cells failed to mature and the expression of surface molecules remained at the level of immature dendritic cells (DC). The antibody itself had no effect on dendritic cell maturation (DC CD51). The results are shown in Figure 13.

When dendritic cells matured with LPS were injected into the footpad of allogeneic C3H/HE mice, they induced a strong allogeneic T-cell response as measured by the increase in weight of the popliteal lymphnode of the right footpad compared to the popliteal lymphnode of the left footpad. By contrast, the increase in weight of the right popliteal lymphnode over that of the left popliteal lymphnode was markedly reduced when dendritic cells were exposed to antiCD51 antibody prior to maturation with LPS. However, the overall increase in weight was still above that of popliteal lympnodes of mice that had been injected with PBS in both footpads. The results are shown in Figure 14.

EXAMPLE 13

Modulation of human dendritic cells *ex vivo*

Agonists of CD36, CD51, thrombospondin receptors or β-integrin may be used to modulate human immune response in patients with unwanted and/or harmful allo- or auto-immune responses. For such a method of treatment immature human dendritic cells which are defined and identifiable as described herein and with the ability to phagocytose are derived from preparations of human peripheral blood. Specifically, the dendritic cells are derived from CD34+ stem cells or monocytes isolated from human peripheral blood by the method described in Example 1. To the preparation of cells suspended in appropriate medium, for example RPMI as defined herein, an agonist of C36, CD51, thrombospondin receptor or β-integrin is added. The relative concentration of agonist to cells is adjusted depending on the nature of the agonist used. For example, if the agonist is a monoclonal antibody, about 25 µg antibody to about 10^6 dendritic cells is appropriate at a concentration of 25 µg $M1^{-1}$. The cells are treated for between 3 and 24 hours.

Depending on the particular application cells are returned to the individual from which they were originally derived or administered to another individual. Adminitration may be by intravenous infusion, by inhalation or by sub-cutaneous or intramuscular injection.

Administration of dendritic cells to a human following the method described above will give rise to a generalized immune suppressive effect which will be useful, in a number of situations, for example in the prevention of rejection of allografts and

xenografts or for treatment of disease suspected of having an auto-immune basis but for which the auto-antigen is not known.

However, the method described above may be modified to produce dendritic cells which are tolerant to a specific antigen. In this case the dendritic cell preparation is exposed to an antigen against which tolerance is to be induced as well as to the CD36, CD51, thrombospondrin receptor or β-integrin agonist. The cells may be exposed to antigenic material, before, after or simultaneously with the aforesaid agonist molecule. The antigenic material may be linked to, fused to or otherwise associated with said agonist molecule. Exposure to the antigenic material is for about 6 to about 24 hours with or without an immune stimulant, then the cells are reintroduced to the patient as described above.

The ability to induce tolerance to a specific antigen, for example an allo, xeno or auto-antigen allows a great many therapeutic applications. For example tolerance can be induced in respect of the following antigens:

to major or minor histocompatibility antigens of a recipient of a bone marrow transplant (to modulate graft versus host disease in bone marrow transplantation in dendritic cells from the bone marrow donor) or

to donor major or minor histocompatibility antigens in dendritic cells of recipients of solid organ transplant or

to antigens to which there is pathological immune response causing auto-immune diseases for example: components of autologous red blood cells to modulate

the immune response in patients with auto-immune hemolytic anaemia
components of autologous platelets in patients with auto-immune thrombocytopeniacomponents of beta islet cells of the pancreas in patients with insulin dependent diabetes mellitus
components of other endocrine organs in patients with other organ specific auto-immune diseases
components of the acetylcholine receptor in patients with myasthenia gravis
other antigens or apoptotic cells containing antigens causing harmful or pathological immune responses in other auto-immune diseases

to antigens to which there is pathological immune response causing atopic or allergic diseases, for example antigens eliciting an immune response in hay fever, asthma, eczema or coeliac disease

to antigens to which there is pathological immune response that may be defined in other diseases for example in non-organ specific immune diseases (systemic lupus erythematosis or rheumatoid arthritis) or other immune mediated arthritis or other connective tissue diseases
in inflammatory bowel disease
in auto-immune hepatitis
in multiple sclerosis
or in other auto-immune disease

to allo-antigens to which there is a harmful or pathological immune response for example components of red blood cells in haemolytic disease of the newborn or in previously transfused patients components of platelets for example in neo-natal allo immune thrombocytopenia or in conditions where there is an allo-immune response to transfused platelets

other blood products or substitutes for example Factor VIII in haemophilia patients
other synthesized or manufactured or naturally occurring products or substances

Although the treatment of humans with dendritic cells is described in this example it will be appreciated that other antigen-presenting cells, such as macrophages, monocytes or β-lymphocytes could be used for treatment with an agonist of CD36, CD51, thrombospondin receptor or β-integrin and optionally an antigenic material. Specific tolerance can be introduced in such cells for use in any of the applications listed above.

Example 14

Preparation of phosphatidylserine liposome compositions and their therapeutic uses.

Liposomes containing phosphatidylserine or other negatively charged phospholipids, with or without additional targeting molecules, induce general immune unresponsiveness. Liposomes encapsulating antigens and phospholipids with or without additional targeting molecules induce antigen specific immune unresponsiveness.

Liposomes are prepared as described by Coradini et al, Anticancer Research 1998 18 177-182. In brief clean glass tubes are coated with 2 micromolar of mixtures of phosphatidylcholine and phosphatidylserine, other negatively charged phospholipids or other phospholipids including cholesterol and/or cholesterol ester dissolved in chloroform. The solvent is evaporated under nitrogen gas and the tubes incubated in a vacuum for 45 minutes. Sterilised phosphate buffered saline

(unmodified liposomes) or containing the antigen(s) to which unresponsiveness will be induced with or without molecules allowing targeting of the liposomes to CD36 and/or CD51 and/or beta-integrins and/or other receptors of apoptotic cells or other molecules expressed on the surface of antigen presenting cells, is added to the lipid shell. Suitable targeting molecules are monoclonal antibodies to the respective receptors or fragments of the P. falciparum erythrocyte membrane protein-1 that bound to CD36 and/or thrombospondin. The tubes are shaken at high speed for 5 minutes and separated from free fatty acid by ultracentrifugation at 100,000g for 60 minutes. Targeting molecules (see above) may be covalently or non-covalently attached to the surface of liposomes. The liposomes are filtered through a 0.22 micrometer filter. Encapsulation of antigens and targeting molecules can also be achieved by freeze-thawing or dehydration/rehydration or by reverse phase evaporation (Monnard PA et al, Biochem. Biophys. Acta 1997 1329 39-50) or by other published methods of preparing liposomes.

Liposomes prepared as described above would be added to 1 x 10^6 isolated immature dendritic cells or to other antigen presenting cells at a concentration of 25 micrograms per ml. The maturation and function of the dendritic cells or other antigen presenting cells is assessed as previously described. The liposomes containing phosphatidylserine (with or without targeting molecules) is used to treat dendritic cells or other antigen presenting cells ex vivo or for systemic treatment.

APPENDIX 1

DI is distributor
SD is standard designation

Other MABs are

OKM5 Ortho Pharmaceutical Corporation
OKM8 1001 US Highway 202
P.O. Box 250
Raritan, N.J.

cd 36 in HDB-D1 HDB-NOND1 http://www.atcc.org/cgi-bin/Sfgat...abase=local%2FHDB-NOND1&text=cd36

Your query was:
cd36

The selected databases contain 18 documents matching your query:

1: 1013396 RE 1.CE>platelet 1.SN>CD36 1.a.CC>differentia
2: 1003558 RE 1.CE>platelet 1.U>cell membrane 1.SN>CD36
3: 1018253 RE 1.SN>CD36 1.a.CC>differentiation 1.b.CC>gly
4: 1020319 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
5: 1013397 RE 1.CE>platelet 1.SN>CD36 1.a.CC>differentia
6: 1020540 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
7: 1017636 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
8: 1022016 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
9: 1019865 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
10: 1024459 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
11: 1019119 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36 1.MW
12: 1009963 RE 1.G>Homo sapiens 1.CN>human 1.CE>monocyte
13: 1016854 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet
14: 1023242 RE 1.G>Homo sapiens 1.CN>human 1.U>cell membr
15: 22825 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet
16: 1012440 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
17: 1012380 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
18: 1003358 RE 1.SN>ACTH 1.FS>N-terminal region 1.a.CC>ho

013396 RE 1.CE>platelet 1.SN>CD36 1.a.CC>differentia

1013396 RE 1.CE>platelet 1.SN>CD36 1.a.CC>differentiation

AN 1013396
DI P>Medica
DI 2382 Camino Vida Roble, Suite I
DI Carlsbad, CA 92009 USA
DI 1-619-438-1886
DE C>CLB/703 ;developer
DE P>MON1118 ;distributor
PD ;IgG1
RE 1.CE>platelet 1.SN>CD36 1.a.CC>differentiation
RE 2.CE>monocyte 2.SN>CD36 2.a.CC>differentiation
RE 3.CE>macrophage 3.SN>CD36 3.a.CC>differentiation
RE 4.CE>platelet 4.SN>CD36 4.a.CC>differentiation
AP ;frozen section

SD MON1118
LD USA BAL
EI DA>9303
CI ;catalog
SN Synonym>CD36 1013396 SN Synonym>CD36

_003558 RE 1.CE>platelet 1.U>cell membrane 1.SN>CD36

1003558 RE 1.CE>platelet 1.U>cell membrane 1.SN>CD36

AN 1003558
DI P>Biodesign International
DI 105 York Street
DI Kennebunkport, ME 04043 USA
DI 1-207-985-1944
DE P>N42540M ;distributor
PD ;IgG1
RE 1.CE>platelet 1.U>cell membrane 1.SN>CD36
RE 1.a.CC>differentiation 1.b.CC>protein
RE 1.c.CC>blood coagulation factor
AV ;purified
SD N42540M
LD USA BAL
EI DA>9002 CV>9007
CI ;catalog
SN Synonym>CD36 1003558 SN Synonym>CD36

018253 RE 1.SN>CD36 1.a.CC>differentiation 1.b.CC>gl

1018253 RE 1.SN>CD36 1.a.CC>differentiation 1.b.CC>glycoprotein

AN 1018253
DI P>BioGenex Laboratories
DI 4600 Norris Canyon Road
DI San Ramon, CA 94583 USA
DI 1-510-275-0550
DI 1-800-421-4149 (toll free USA)
DE P>1E8 ;distributor
DO G>Mus musculus CN>mouse
RE 1.SN>CD36 1.a.CC>differentiation 1.b.CC>glycoprotein
AV ;purified
SD 1E8
LD USA JMJ
EI DA>9602
CI ;catalog
SN Synonym>CD36 1018253 SN Synonym>CD36

020319 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36

1020319 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36

AN 1020319
DI P>Harlan Bioproducts for Science, Inc.
DI P.O. Box 29176
DI Indianapolis, IN 46229-0176
DI 1-317-894-7536
DI 1-800-9-SCIENCE
DE C>89 ;distributor
DE P>MCA1214 ;distributor
DO G>Mus musculus CN>mouse
PD ;IgG2b
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
RE 1.a.CC>differentiation
AP ;flow cytometry ;Western blot
AV ;purified
SD 89
SD MCA1214
LD USA CLB
EI DA>9702
CI ;catalog
SN Synonym>CD36 1020319 SN Synonym>CD36

013397 RE 1.CE>platelet 1.SN>CD36 1.a.CC>differentia

1013397 RE 1.CE>platelet 1.SN>CD36 1.a.CC>differentiation

AN 1013397
DI P>Caltag Laboratories
DI 1849 Bayshore Blvd. #200
DI Burlingame, CA 94010
DI 1-650-652-0468
DI 1-800-874-4007
DI 2.P>Medica
DI 2382 Camino Vida Roble, Suite I
DI Carlsbad, CA 92009 USA
DI 1-619-438-1886
DE C>VM58 ;developer
DE P>MON1143 ;distributor
DE P>VM58 ;distributor
DE 2.P>MON1143 ;distributor
PD ;IgG1
RE 1.CE>platelet 1.SN>CD36 1.a.CC>differentiation
RE 2.CE>monocyte 2.SN>CD36 2.a.CC>differentiation
RE 3.CE>macrophage 3.SN>CD36 3.a.CC>differentiation
RE 4.CE>platelet 4.SN>CD36 4.a.CC>differentiation
AP ;frozen section

SD VM58
LD USA BAL
EI DA>9303
CI ;catalog
SN Synonym>CD36 1013397 SN Synonym>CD36

_020540 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36

1020540 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36

AN 1020540
DI P>Harlan Bioproducts for Science, Inc.
DI P.O. Box 29176
DI Indianapolis, IN 46229-0176
DI 1-317-894-7536
DI 1-800-9-SCIENCE
DE P>89 ;developer
DE P>MCA1214 ;distributor
DO G>Mus musculus CN>mouse
PD ;IgG2b
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
RE 1.a.CC>differentiation
AP ;flow cytometry ;Western blot
AV ;purified
SD 89
SD MCA1214
LD USA CLB
EI DA>9702
CI ;catalog
SN Synonym>CD36 1020540 SN Synonym>CD36

1017636 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36

1017636 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36

AN 1017636
DI P>Novocastra Laboratories Ltd.
DI 24 Claremont Place
DI Newcastle upon Tyne NE2 4AA, UK
DI 44-0191 222 8550
DE P>NCL-CD36 ;distributor
DE P>SMO ;distributor
DO G>Mus musculus CN>mouse
AS ;immunohistochemical staining
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
RE 1.a.CC>differentiation
AP ;frozen section
AV ;ascites
SD NCLCD36
SD SMO
LD USA BAL
EI DA>9904
CI ;catalog
SN Synonym>CD36 1017636 SN Synonym>CD36

022016 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36

1022016 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36

AN 1022016
DI P>O.E.M. Concepts, Inc.
DI 1889 Route 9, Bldg. 25, Unit 96
DI Toms River, NJ 08755 USA
DI 1-732-341-3570
DE C>289-10930 ;distributor
DE P>M2-L69 ;distributor
DO G>Mus musculus CN>mouse
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
RE 1.a.CC>differentiation
AP ;cell surface marker
AV ;purified
SD 28910930
SD M2L69
LD USA EJK
EI DA>9712
CI ;catalog
SN Synonym>CD36 1022016 SN Synonym>CD36

019865 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36

1019865 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36

AN 1019865
DI P>Upstate Biotechnology, Inc.
DI 199 Saranac Avenue
DI Lake Placid, NY 12946 USA
DI 1-617-890-8845
DI 1-800-233-3991 (toll free USA) (sales)
DE P>05-287 ;distributor
DO G>Mus musculus CN>mouse S>BALB/c O>spleen
PD ;IgM
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
RE 1.a.CC>differentiation 1.b.CC>protein
AP ;immunocytochemistry
AV ;ascites
SD 05287
LD USA JMJ
EI DA>9611
CI ;catalog
SN Synonym>CD36 1019865 SN Synonym>CD36

016854 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet

1009963 RE 1.G>Homo sapiens 1.CN>human 1.CE>monocyte

1009963 RE 1.G>Homo sapiens 1.CN>human 1.CE>monocyte 1.SN>CD36

AN 1009963
DI P>Harlan Bioproducts for Science, Inc.
DI P.O. Box 29176
DI Indianapolis, IN 46229-0176
DI 1-317-894-7536
DI 1-800-9-SCIENCE
DI 2.P>Immunotech S.A.
DI Departement commercial
DI Luminy Case 915
DI 13288 Marseille Cedex 9, France
DI 33-91-41-41-38
DI 430246 F IMMTECH
DE C>Fa6-152 ;developer
DE P>MCA 682 ;distributor
DE 2.P>0765 ;distributor
DE 2.P>0766 ;distributor
DE 2.P>FA6.152 ;distributor
DO G>Mus musculus CN>mouse
PD ;IgG1
RE 1.G>Homo sapiens 1.CN>human 1.CE>monocyte 1.SN>CD36
RE 1.a.CC>differentiation
RE 2.G>Homo sapiens 2.CN>human 2.CE>macrophage 2.SN>CD36
RE 2.a.CC>differentiation
RE 3.G>Homo sapiens 3.CN>human 3.CE>platelet 3.SN>CD36
RE 3.a.CC>differentiation
AV ;purified ;2.fluorescein conjugate ;2.purified
SD 0765
SD 0766
SD FA6152
SD MCA682
LD USA BAL
EI DA>9103 CV>9104
CI ;catalog
SN Synonym>CD36 1009963 SN Synonym>CD36

_023242 RE 1.G>Homo sapiens 1.CN>human 1.U>cell membr

1023242 RE 1.G>Homo sapiens 1.CN>human 1.U>cell membrane 1.SN>CD36

AN 1023242
SO Exp Cell Res 1992;198:85-92
SO J Exp Med 1990;171:1883-92
DI P>Lab Vision-NeoMarkers
DI 47770 Westinghouse Drive
DI Fremont, CA 94539 USA
DI 1-800-828-1628
DE C>1A7 ;distributor
DE P>MS-466-P ;distributor
IM G>Homo sapiens CN>human CE>platelet SN>CD36 a.CC>differentiation
IM b.CC>glycoprotein c.CC>receptor
DO G>Mus musculus CN>mouse
PD ;IgG2b ;kappa
RE 1.G>Homo sapiens 1.CN>human 1.U>cell membrane 1.SN>CD36
RE 1.MW>88 kD 1.a.CC>differentiation 1.b.CC>glycoprotein
RE 1.c.CC>receptor
AP ;flow cytometry ;immunofluorescence ;immunoprecipitation
AP ;Western blot ;immunohistology ;gold labelling

AB platelet GPIIIb, platelet glycoprotein IIIb, and OKM5-antigen.
SD 1A7
SD MS466P
LD USA MCM
EI DA>9806
CI ;catalog
SN Synonym>CD36 1023242 SN Synonym>CD36

?825 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet

22825 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet

AN 22825
AU Kemshead J
AD Imperial Cancer Research Technology;
AD Sardinia House;
AD Sardinia Street;
AD London WC2A 3NL;
AD UK;
AD Tel 01 242 1136;
AD TELEX 265107 TCRFG;
AD FAX 01 831 4991
SO Br J Haematol 1984;57:621
DE P>M148 ;developer
IM G>Homo sapiens 1.CN>human PA>medulloblastoma a.CC>neoplasm
PD ;IgG1
RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet
RE 1.U>cell surface 1.SN>CD36 1.MW>110-130 kD
RE 1.a.CC>differentiation
RE 2.G>Homo sapiens 2.CN>human 2.PA>medulloblastoma
RE 2.a.CC>neoplasm
RE 3.G>Homo sapiens 3.CN>human 3.PA>neuroblastoma
RE 3.a.CC>neoplasm
RE 4.G>Homo sapiens 4.CN>human 4.PA>rhabdomyosarcoma
RE 4.a.CC>neoplasm
AP ;immunofluorescence ;immunoprecipitation
AB in vivo imaging and therapy
SD M148
LD EUR BD FI>EUR0003951 EUR901.TXT
EI DA>8901 CV>8904
CI ;catalog
SN Synonym>CD36 22825 SN Synonym>CD36

1012380 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36

1012380 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36

AN 1012380
DI P>Biodesign International
DI 105 York Street
DI Kennebunkport, ME 04043 USA
DI 1-207-985-1944
DI 2.P>Harlan Bioproducts for Science, Inc.
DI P.O. Box 29176
DI Indianapolis, IN 46229-0176
DI 1-317-894-7536
DI 1-800-9-SCIENCE
DI 3.P>Lampire Biological Laboratories
DI P.O. Box 270
DI Pipersville, PA 18947 USA
DI 1-215-795-2838
DI 4.P>Sigma Chemical Company
DI P.O. Box 14508
DI St. Louis, MO 63178 9916 USA
DI 1-800-325-3010 (toll free USA)
DI 1-314-771-5750
DE C>SM0 ;developer
DE P>P54168M ;distributor
DE P>SMO ;distributor
DE 2.P>MCA-722F ;discontinued designation
DE 2.P>MCA722 ;distributor
DE 2.P>SMO ;distributor
DE 3.P>LBL 268 ;distributor
DE 3.P>SM0 ;distributor
DE 4.P>C 4679 ;distributor
DE 4.P>F5898 ;distributor
DE 4.P>P9312 ;distributor
DE 4.P>R6395 ;distributor
DE 4.P>SMO ;distributor
DO G>Mus musculus CN>mouse
PD ;IgM
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
RE 1.a.CC>differentiation
AV ;purified ;2.purified ;4.fluorescein conjugate
AV ;4.phycoerythrin conjugate
SD C4679
SD F5898
SD LBL268
SD MCA722
SD MCA722F
SD P54168M
SD P9312
SD R6395
SD SM0
SD SMO
LD USA BAL
EI DA>9803 CV>9111
CI ;catalog
SN Synonym>CD36 1012380 SN Synonym>CD36

1003558 RE 1.CE>platelet 1.U>cell membrane 1.SN>CD36

1003558 RE 1.CE>platelet 1.U>cell membrane 1.SN>CD36

AN 1003558
DI P>Biodesign International
DI 105 York Street
DI Kennebunkport, ME 04043 USA
DI 1-207-985-1944
DE P>N42540M ;distributor
PD ;IgG1
RE 1.CE>platelet 1.U>cell membrane 1.SN>CD36
RE 1.a.CC>differentiation 1.b.CC>protein
RE 1.c.CC>blood coagulation factor
AV ;purified
SD N42540M
LD USA BAL
EI DA>9002 CV>9007
CI ;catalog
SN Synonym>CD36 1003558 SN Synonym>CD36

1024459 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36

1024459 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36

DI P>Biogenesis Ltd.
DI 7 New Fields
DI Stinsford Road
DI Poole BH17 7NF, England
DI UK
DI 44-1202 660006
DE C>SM-phi IgM ;distributor
DE P>2125-3607 ;distributor
DO G>Mus musculus CN>mouse
PD ;Ig
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
RE 1.a.CC>differentiation
AP ;immunofluorescence
AV ;fluorescein conjugate
AB CD36 is also known as platelet GPIV, GPIV, platelet GPIIIb, GPIIIb, platelet
AB glycoprotein IV, and FAT (rat).
SD 21253607
SD SMPHIIGM
LD USA MCM
EI DA>9811
CI ;catalog
SN Synonym>CD36 1024459 SN Synonym>CD36

1016854 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet

1016854 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet

AN 1016854
DI P>PharMingen
DI 10975 Torreyana Road
DI San Diego, CA 92121 USA
DI 1-619-677-7737
DI 1-800-848-6227 (toll free USA)
DE P>CB38 ;distributor
DO G>Mus musculus CN>mouse S>BALB/c
PD ;IgM ;kappa
RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet
RE 1.U>cell membrane 1.SN>CD36 1.MW>88 kD
RE 1.a.CC>differentiation 1.b.CC>glycoprotein
AP ;flow cytometry ;immunoprecipitation
AV ;fluorescein conjugate ;purified
SD CB38
LD USA JMJ
EI DA>9504
CI ;catalog
SN Synonym>CD36 1016854 SN Synonym>CD36

1012440 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36

1012440 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36

AN 1012440
DI P>BioSource International
DI 820 Flynn Roa
DI Camarillo, CA 93012 USA
DI 1-800-242-0607(toll free USA)
DI 1-805-987-0086
DI 2.P>Cymbus Bioscience Limited
DI 2 Venture Road
DI Chilworth Research Center
DI Southampton, Hampshire SO1 7NS UK
DI 44-703-767178
DI 3.P>Roche Molecular Biochemicals
DI formerly Boehringer Mannheim GmbH
DI Sandhofer Strasse 116
DI D-68305 Mannheim Germany
DI 49-621-759 8577
DE C>SMO ;developer
DE P>AHS3601 ;distributor
DE P>AHS3608 ;distributor
DE P>CS-CD36-FI ;discontinued designation
DE P>CS-CD36-UN ;discontinued designation
DE P>SMO ;distributor
DE 2.P>CBL 168 ;distributor
DE 2.P>SMO ;distributor
DE 3.P>1441 230 ;discontinued designation
DE 3.P>1441 264 ;distributor
DE 3.P>SMO ;distributor
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36
RE 1.a.CC>differentiation
AV ;fluorescein conjugate ;3.purified
SD 1441230
SD 1441264
SD AHS3601
SD AHS3608
SD CBL168
SD CSCD36FI
SD CSCD36UN
SD SMO
LD USA BAL
EI DA>9709 CV>9111
CI ;catalog
SN Synonym>CD36 1012440 SN Synonym>CD36

1003358 RE 1.SN>ACTH 1.FS>N-terminal region 1.a.CC>ho

1003358 RE 1.SN>ACTH 1.FS>N-terminal region 1.a.CC>hormone

AN 1003358
DI P>Biodesign International
DI 105 York Street
DI Kennebunkport, ME 04043 USA
DI 1-207-985-1944
DI 2.P>Cymbus Bioscience Limited
DI 2 Venture Road
DI Chilworth Research Center
DI Southampton, Hampshire SO1 7NS UK
DI 44-703-767178
DE C>58 ;developer
DE P>E54008M ;distributor
RE 1.SN>ACTH 1.FS>N-terminal region 1.a.CC>hormone
AV ;purified
AB CD36 is also known as GPIIIb, GPIV
SD 58
SD E54008M
LD USA BAL
EI DA>9002 CV>9007
CI ;catalog
SN Synonym>ACTH

1019119 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36 1.MW

1019119 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36 1.MW>88 kD

AN 1019119
SO J Cell Biol 1994;269:6011
SO J Cell Biol 1993;268:16179
DI P>Transduction Laboratories
DI 133 Venture Ct., Suite 5
DI Lexington, Ky 40511-9923
DI 1-606-259-1550
DI 1-800-227-4063
DE P>73 ;distributor
DE P>C23620 ;distributor
IM G>Homo sapiens CN>human SN>CD36 FS>amino acids 70-242
IM a.CC>protein
DO G>Mus musculus CN>mouse
PD ;IgG2a
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD36 1.MW>88 kD
RE 1.a.CC>protein
RE 2.G>Rattus norvegicus 2.CN>Norway rat 2.SN>CD36
RE 2.MW>88 kD 2.a.CC>protein
RE 3.G>Gallus gallus 3.CN>chicken 3.SN>CD36 3.MW>88 kD
RE 3.a.CC>protein
AP ;Western blot ;immunofluorescence
AV ;purified
SD 73
SD C23620
LD USA JMJ
EI DA>9901
CI ;catalog
SN Synonym>CD36 1019119 SN Synonym>CD36

APPENDIX 2

DI is distributor
SD is standard designation

1022961 RE 1.SN>CD51 1.a.CC>differentiation

1022961 RE 1.SN>CD51 1.a.CC>differentiation

AN 1022961
DI P>Caltag Laboratories
DI 1849 Bayshore Blvd. #200
DI Burlingame, CA 94010
DI 1-650-652-0468
DI 1-800-874-4007
DE C>NGX-IV/110 ;distributor
DE P>MON1027 ;distributor
RE 1.SN>CD51 1.a.CC>differentiation

SD NGXIV110
LD USA MCM
EI DA>9805
CI ;catalog

1022017 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51/61 c

1022017 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51/61 c

AN 1022017
DI P>O.E.M. Concepts, Inc
DI 1889 Route 9, Bldg. 25, Unit 96
DI Toms River, NJ 08755 USA
DI 1-732-341-3570
DE C>289-12336 ;distributor
DE P>M2-L69 ;distributor
DO G>Mus musculus CN>mouse
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51/61 complex
RE 1.a.CC>differentiation
AP ;cell surface marker
AV ;purified
AB Reactant#1: CD51/61 complex is also known as integrin alpha V beta 3.
SD 28912336
SD M2L69
LD USA EJK
EI DA>9712
CI ;catalog
SN Synonym>CD51/61 complex 1022018 ****HB/HYBRID

1013413 RE 1.CE>platelet 1.SN>CD51 1.a.CC>differentiation

1013413 RE 1.CE>platelet 1.SN>CD51 1.a.CC>differentiation

AN 1013413
DI P>Medica
DI 2382 Camino Vida Roble, Suite I
DI Carlsbad, CA 92009 USA
DI 1-619-438-1886
DE C>706 ;developer
DE P>MON1130 ;distributor
PD ;IgG1
RE 1.CE>platelet 1.SN>CD51 1.a.CC>differentiation

SD MON1130
LD USA BAL
EI DA>9303
CI ;catalog

1024461 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51

1024461 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51

AN 1024461
DI P>Biogenesis Ltd.
DI 7 New Fields
DI Stinsford Road
DI Poole BH17 7NF, England
DI UK
DI 44-1202 660006
DE C>13C2 ;distributor
DE P>2125-5108 ;distributor
DE P>2125-5114 ;distributor
DE P>2125-5119 ;distributor
DO G>Mus musculus CN>mouse
PD ;Ig
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51
RE 1.a.CC>differentiation
AP ;immunofluorescence
AV ;R-phycoerythrin conjugate ;fluorescein conjugate
AB CD51 is also known as integrin alpha V subunit and vitronectin receptor
AB alpha subunit.
SD 13C2
SD 21255108
SD 21255114
SD 21255119
LD USA MCM
EI DA>9811
CI ;catalog

1017037 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51

1017037 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51

DI P>Zymed Laboratories Inc.
DI 458 Carlton Court
DI South San Francisco, CA 94080 USA
DI 1-800-874-4494 (toll free USA)
DI 1-415-871-4494
DE P>07-5103 ;distributor
DE P>NK1-M9 ;distributor
DO G>Mus musculus CN>mouse S>BALB/c
PD ;IgG1
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51
RE 1.a.CC>differentiation 1.b.CC>protein
AP ;flow cytometry ;immunofluorescence
AV ;purified
SD 075103
SD NK1M9
LD USA JMJ
EI DA>9708
CI ;catalog

1009962 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51

1009962 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51

AN 1009962
DI P>Biodesign International
DI 105 York Street
DI Kennebunkport, ME 04043 USA
DI 1-207-985-1944
DI 2.P>Harlan Bioproducts for Science, Inc.
DI P.O. Box 29176
DI Indianapolis, IN 46229-0176
DI 1-317-894-7536
DI 1-800-9-SCIENCE
DE C>AMF7 ;developer
DE P>AMF7 ;distributor
DE P>P42770M ;distributor
DE 2.P>MCA 683 ;distributor
DO G>Mus musculus CN>mouse
PD ;IgG1
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51
RE 1.a.CC>differentiation
AV ;purified ;2.purified
SD AMF7
SD MCA683
SD P42770M
LD USA BAL
EI DA>9103 CV>9104
CI ;catalog

1021411 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet

1021411 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet 1.SN>CD51

AN 1021411
DI P>Immunotech S.A.
DI Departement commercial
DI Luminy Case 915
DI 13288 Marseille Cedex 9, France
DI 33-91-41-41-38
DI 430246 F IMMTECH
DE C>69-6-5 ;distributor
DE P>1603 ;distributor
DO G>Mus musculus CN>mouse S>BALB/c O>spleen
PD ;IgG2a
RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet 1.SN>CD51
RE 1.a.CC>protein
AV ;purified
SD 1603
SD 6965
LD USA JMJ
EI DA>9707
CI ;catalog

1015384 RE 1.G>Mus musculus 1.CN>mouse 1.SN>CD51

1015384 RE 1.G>Mus musculus 1.CN>mouse 1.SN>CD51

AN 1015384
DI P>PharMingen
DI 10975 Torreyana Road
DI San Diego, CA 92121 USA
DI 1-619-677-7737
DI 1-800-848-6227 (toll free USA)
DE C>H9.2B8 ;developer
DE P>01520D ;distributor
DE P>01521D ;distributor
DE P>01522D ;distributor
DE P>01525B ;distributor
DO G>Cricetulus sp. CN>hamster
IP G>Mus musculus CN>mouse
PD ;IgG
RE 1.G>Mus musculus 1.CN>mouse 1.SN>CD51
RE 1.a.CC>differentiation
AP ;flow cytometry ;immunofluorescence
AV ;biotin conjugate ;fluorescein conjugate
AV ;phycoerythrin conjugate ;purified
SD 01520D
SD 01521D
SD 01522D
SD 01524D
SD 01525B
SD H92B8
LD USA BAL
EI DA>9408
CI ;catalog

1023962 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51

1023962 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51

AN 1023962
SO Cell 1992;69:11-25
DI P>Ancell Corporation
DI 243 Third Street North
DI P.O. Box 87
DI Bayport, MN 55003 USA
DI 1-800-374-9523 (toll free USA)
DI 1-612-439-0835
DE C>P2W7 ;distributor
DE P>202-020 ;distributor
DE P>202-030 ;distributor
DE P>202-040 ;distributor
DE P>202-050 ;distributor
IM G>Homo sapiens CN>human O>eye PA>melanoma CD>V+B2 a.CC>neoplasm
DO G>Mus musculus CN>mouse
PD ;IgG1 ;kappa
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51
RE 1.a.CC>differentiation
AP ;immunoprecipitation ;flow cytometry ;frozen section
AV ;R-phycoerythrin conjugate ;biotin conjugate
AV ;fluorescein conjugate ;purified
SD 202020
SD 202030
SD 202040
SD 202050
SD P2W7
LD USA MCM
EI DA>9808
CI ;catalog

1023559 RE 1.G>Mus musculus 1.CN>mouse 1.SN>integrin

1023559 RE 1.G>Mus musculus 1.CN>mouse 1.SN>integrin alpha V

SO Biochemistry 1990;29:10191
SO Exp Cell Res 1993;205:25
DI P>Upstate Biotechnology, Inc.
DI 199 Saranac Avenue
DI Lake Placid, NY 12946 USA
DI 1-617-890-8845
DI 1-800-233-3991 (toll free USA) (sales)
DE P>05-437 ;distributor
DO G>Mus musculus CN>mouse
RE 1.G>Mus musculus 1.CN>mouse 1.SN>integrin alpha V
RE 1.MW>160 kD 1.a.CC>differentiation 1.b.CC>receptor
AP ;Western blot ;immunoprecipitation ;immunohistochemistry
AV ;ascites
AB Reactant is also known as vitronectin receptor alpha subunit and CD51.
SD 05437
LD USA MCM
EI DA>9807
CI ;catalog

1023927 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin

1023927 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin alpha V

AN 1023927
SO J Biol Chem 1994;269:6940
DI P>Chemicon International, Inc.
DI 28835 Single Oak Dr.
DI Temecula, CA 92590 USA
DI 1-909-676-8080
DI 1-800-437-7500(toll free USA)
DE C>P3G8 ;distributor
DE P>MAB1953 ;distributor
IM G>Homo sapiens CN>human O>lung PA>carcinoma a.CC>neoplasm
DO G>Mus musculus CN>mouse
PD ;IgG1
RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin alpha V
RE 1.a.CC>differentiation 1.b.CC>receptor
AP ;immunocytology ;immunohistochemistry ;immunoprecipitation
AP ;flow cytometry ;ELISA ;FACS
AV ;purified
AB Reactant is also known as CD51 and vitronectin receptor alpha subunit.
AB Product reacts with all alpha V-containing integrin receptors.
AB Product will react with some lymphoid cell lines (B cells), many carcinoma and
AB melanoma cell lines and osteosarcomas.
SD MAB1953
SD P3G8
LD USA MCM
EI DA>9808
CI ;catalog

1015432 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51 1.FS

1015432 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51 1.FS>alpha subunit

AN 1015432
DI P>Biodesign International
DI 105 York Street
DI Kennebunkport, ME 04043 USA
DI 1-207-985-1944
DI 2.P>Caltag Laboratories
DI 1849 Bayshore Blvd. #200
DI Burlingame, CA 94010
DI 1-650-652-0468
DI 1-800-874-4007
DI 3.P>Cymbus Bioscience Limited
DI 2 Venture Road
DI Chilworth Research Center
DI Southampton, Hampshire SO1 7NS UK
DI 44-703-767178
DI 4.P>Endogen Inc.
DI 30 Commerce Way
DI Woburn, MA 01801-1059 USA
DI 1-781-937-0890
DI 5.P>Genosys Biotechnologies, Inc.
DI 1442 Lake Front Circle, Suite 185
DI The Woodlands, TX 77380-3600 USA
DI 1-713-363-3693
DI 1-800-234-5362 (toll free USA)
DI 6.P>Harlan Bioproducts for Science, Inc.
DI P.O. Box 29176
DI Indianapolis, IN 46229-0176
DI 1-317-894-7536
DI 1-800-9-SCIENCE
DI 7.P>Lampire Biological Laboratories
DI P.O. Box 270
DI Pipersville, PA 18947 USA
DI 1-215-795-2838
DI 8.P>PharMingen
DI 10975 Torreyana Road
DI San Diego, CA 92121 USA
DI 1-619-677-7737
DI 1-800-848-6227 (toll free USA)
DI 9.P>T Cell Diagnostics, Inc.
DI 6 Gill Street
DI Woburn, MA 01801-1721 USA
DI 1-800-624-4021
DI 1-617-937-9587
DE C>23C6 ;developer
DE P>23C6 ;distributor
DE P>P54490M ;distributor
DE 2.P>23C6 ;distributor
DE 2.P>MON1167 ;distributor
DE 3.P>23C6 ;distributor
DE 3.P>CBL490 ;distributor
DE 4.P>23C6 ;distributor
DE 4.P>MA-5100 ;distributor
DE 5.P>23C6 ;distributor
DE 5.P>AM-19-760 ;distributor
DE 6.P>23C6 ;distributor
DE 6.P>MCA-757 ;discontinued designation

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DE 6.P>MCA757G ;distributor
DE 7.P>23C6 ;distributor
DE 7.P>LBL 590 ;distributor
DE 8.P>23C6 ;distributor
DE 8.P>31561A ;distributor
DE 8.P>31564X ;distributor
DE 9.P>23C6 ;distributor
DE 9.P>IA1S04 ;distributor
DO G>Mus musculus CN>mouse
PD ;IgG1
RE 1.G>Homo sapiens 1.CN>human 1.SN>CD51 1.FS>alpha subunit
RE 1.MW>125 kD 1.a.CC>differentiation
AV ;purified ;4.purified ;6.purified ;8.fluorescein conjugate
AV ;8.purified ;9.supernatant
SD 23C6
SD 31561A
SD 31564X
SD AM19760
SD CBL490
SD IA1S04
SD LBL590
SD MA5100
SD MCA757
SD MCA757G
SD MON1167
SD P54490M
LD USA BAL
EI DA>9706
CI ;catalog
```

1011348 RE 1.G>Homo sapiens 1.CN>human 1.SN>vitronect

1011348 RE 1.G>Homo sapiens 1.CN>human 1.SN>vitronectin receptor

AN 1011348
DI P>Chemicon International, Inc.
DI 28835 Single Oak Dr.
DI Temecula, CA 92590 USA
DI 1-909-676-8080
DI 1-800-437-7500(toll free USA)
DE P>CLB-706 ;distributor
DE P>MAB1980 ;distributor
RE 1.G>Homo sapiens 1.CN>human 1.SN>vitronectin receptor
RE 1.a.CC>receptor
AV ;purified
AB beta subunit of vitronectin receptor referred to as CD51 also
AB Reactant#1: vitronectin receptor beta subunit syn. for CD51
SD CLB706
SD MAB1980
LD USA BAL
EI DA>9107 CV>9108
CI ;catalog
SN Synonym>vitronectin receptor

APPENDIX 3

DI is distributor
SD is standard designation

Beta 5

1019741 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin beta 5
AN 1019741
DI P>Upstate Biotechnology, Inc.
DI 199 Saranac Avenue
DI Lake Placid, NY 12946 USA
DI 1-617-890-8845
DI 1-800-233-3991 (toll free USA) (sales)
DE C>B5-IVF2 ;distributor
DE P>05-283 ;distributor
DO G>Mus musculus CN>mouse S>BALB/c O>spleen
PD ;IgG1
RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin beta 5
RE 1.a.CC>protein
AP ;immunocytochemistry ;blocks cell adhesion
AV ;ascites
SD 05283
SD B5IVF2
LD USA JMJ
EI DA>9611
CI ;catalog

Beta 3

```
1011332 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin beta 3
 AN 1011332
 DI P>Chemicon International, Inc.
 DI 28835 Single Oak Dr.
 DI Temecula, CA 92590 USA
 DI 1-909-676-8080
 DI 1-800-437-7500(toll free USA)
 DE P>MAB1974 ;distributor
 PD ;IgG1
 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin beta 3
 RE 1.a.CC>receptor
 AV ;ascites
 SD MAB1974
 LD USA BAL
 EI DA>9107 CV>9108
 CI ;catalog
```

```
1014236 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin beta 3
 AN 1014236
 AU Ylanne J
 SO Blood 1989;72:1478-86
 SO Blood 1990;76:570-7
 DI P>Biohit OY
 DI Verkkosaarenkatu 4
 DI 00580 Helsinki, Finland
 DI 358-0-773-2900
 DI 2.P>Harlan Bioproducts for Science, Inc.
 DI P.O. Box 29176
 DI Indianapolis, IN 46229-0176
 DI 1-317-894-7536
 DI 1-800-9-SCIENCE
 DI 3.P>ICN Biomedicals
 DI Biomedical Research Products
 DI 3300 Hyland Avenue
 DI Costa Mesa, CA 92626
 DI 1-800-854-0530 (toll free USA)
 DI 1-714-545-0100
 DI 4.P>Locus Genex Oy
 DI Verkkosaarenkatu 4
 DI 00580 Helsinki, Finland
 DI 358-9-773-861
 DE C>BB10 ;developer
 DE P>M-9006000 ;distributor
 DE P>M-9006100 ;distributor
 DE 2.P>MCA-781 ;distributor
 DE 2.P>bb10 ;distributor
 DE 3.P>69-323-1 ;distributor
 DE 3.P>69-323-2 ;distributor
 DE 3.P>BB10 ;distributor
 DE 4.P>BB10 ;distributor
 DE 4.P>M-9006000 ;distributor
 DE 4.P>M-9006100 ;distributor
 IM G>Homo sapiens CN>human SN>CD41 ;purified a.CC>differentiation
 RM ;in vivo
 DO G>Mus musculus CN>mouse S>BALB/c O>spleen
 IP G>Mus musculus CN>mouse PA>myeloma
 PD ;IgG1
 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin beta 3
 RE 1.a.CC>receptor
 RE 2.G>Homo sapiens 2.CN>human 2.SN>platelet GPIIIa
 RE 2.a.CC>blood coagulation factor
 AP ;immunoassay ;not paraffin section ;immunohistochemical staining
 AP ;immunoblotting
 AV ;purified ;2.purified ;3.purified ;4.purified
 SD 693231
 SD 693232
 SD BB10
 SD M9006000
 SD M9006100
 SD MCA781
 LD USA BAL
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EI DA>9711
SN Synonym>CD41 1014236 SN Synonym>CD41

1014281 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin beta 3
AN 1014281
DI P>Bio-Science Products AG
DI Gerliswilstrasse 43
DI Postfach 1173
DI CH-6020 Emmenbrucke, Switzerland
DI 41-555875
DE P>0121022 ;distributor
RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin beta 3
RE 1.a.CC>receptor
RE 2.G>Homo sapiens 2.CN>human 2.SN>CD41
RE 2.a.CC>differentiation
AP ;immunoassay ;immunoblotting ;not paraffin section
AP ;immunohistochemical staining
LD USA BAL
EI DA>9305
CI ;catalog
SN Synonym>CD41 1014281 SN Synonym>CD41

```
1019109 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin beta 3
 AN 1019109
 SO J Cell Biol 1993;122:223
 SO J Cell Biol 1993;121:689
 DI P>Transduction Laboratories
 DI 133 Venture Ct., Suite 5
 DI Lexington, Ky 40511-9923
 DI 1-606-259-1550
 DI 1-800-227-4063
 DE P>26 ;distributor
 DE P>I19620 ;distributor
 IM G>Mus musculus CN>mouse SN>integrin beta 3 FS>amino acids 16-223
 IM a.CC>protein
 DO G>Mus musculus CN>mouse
 PD ;IgM
 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin beta 3
 RE 1.MW>90 kD 1.a.CC>protein
 RE 2.G>Canis familiaris 2.CN>dog 2.SN>integrin beta 3
 RE 2.MW>90 kD 2.a.CC>protein
 RE 3.G>Rattus norvegicus 3.CN>Norway rat 3.SN>integrin beta 3
 RE 3.MW>90 kD 3.a.CC>protein
 RE 4.G>Mus musculus 4.CN>mouse 4.SN>integrin beta 3
 RE 4.MW>90 kD 4.a.CC>protein
 RE 5.G>Gallus gallus 5.CN>chicken 5.SN>integrin beta 3
 RE 5.MW>90 kD 5.a.CC>protein
 AP ;Western blot
 AV ;purified
 SD 26
 SD I19620
 LD USA JMJ
 EI DA>9705
 CI ;catalog
```

1023930 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin beta 3
AN 1023930
SO Cell 1986;45:269-80
DI P>Chemicon International, Inc.
DI 28835 Single Oak Dr.
DI Temecula, CA 92590 USA
DI 1-909-676-8080
DI 1-800-437-7500(toll free USA)
DE C>25E11 ;distributor
DE P>MAB1957 ;distributor
IM T>blood CE>mononuclear cell CS>activated
DO G>Mus musculus CN>mouse
PD ;IgG2a
RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin beta 3
RE 1.a.CC>differentiation 1.b.CC>receptor
RE 2.SN>CD41/CD61 complex 2.a.CC>protein
RE 3.G>Homo sapiens 3.CN>human 3.CE>monoblast 3.PA>leukemia
RE 3.CD>U937 3.SN>CD41/CD61 complex 3.a.CC>protein
AP ;Western blot ;immunocytology ;immunoprecipitation
AP ;flow cytometry
AV ;purified a.PM>protein A chromatography
AB Integrin beta 3 is also known as CD61, GPIIIa, and vitronectin
AB receptor beta chain.
SD 25E11
SD MAB1957
LD USA MCM
EI DA>9808
CI ;catalog

```
1024059 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet 1.SN>CD61
 AN 1024059
 DI P>PharMingen
 DI 10975 Torreyana Road
 DI San Diego, CA 92121 USA
 DI 1-619-677-7737
 DI 1-800-848-6227 (toll free USA)
 DE C>VI-PL2 ;distributor
 DE P>33821 ;distributor
 DE P>33824 ;distributor
 DE P>33825 ;distributor
 DO G>Mus musculus CN>mouse
 PD ;IgG1 ;kappa
 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet 1.SN>CD61
 RE 1.MW>105 kD 1.a.CC>differentiation 1.b.CC>glycoprotein
 RE 2.G>Homo sapiens 2.CN>human 2.CE>megakaryocyte 2.SN>CD61
 RE 2.MW>105 kD 2.a.CC>differentiation 2.b.CC>glycoprotein
 RE 3.G>Homo sapiens 3.CN>human 3.CE>osteoclast 3.SN>CD61
 RE 3.MW>105 kD 3.a.CC>differentiation 3.b.CC>glycoprotein
 RE 4.G>Homo sapiens 4.CN>human 4.T>endothelium 4.SN>CD61
 RE 4.MW>105 kD 4.a.CC>differentiation 4.b.CC>glycoprotein
 XR 1.G>Canis sp. 1.CN>dog 1.SN>CD61 1.a.CC>differentiation
 XR 1.b.CC>glycoprotein
 XR 2.G>Felis sp. 2.CN>cat 2.SN>CD61 2.a.CC>differentiation
 XR 2.b.CC>glycoprotein
 NR 1.G>Sus sp. 1.CN>swine 1.SN>CD61 1.a.CC>differentiation
 NR 1.b.CC>glycoprotein
 AP ;acetone fixed ;frozen section
 AV ;R-phycoerythrin conjugate ;biotin conjugate
 AV ;fluorescein conjugate ;purified
 AB CD61 is also known as integrin beta 3 subunit.
 SD 33821
 SD 33824
 SD 33825
 SD VIPL2
 LD USA MCM
 EI DA>9809
 CI ;catalog
```

```
1011347 RE 1.G>Homo sapiens 1.CN>human 1.SN>vitronectin receptor
 AN 1011347
 DI P>Chemicon International, Inc.
 DI 28835 Single Oak Dr.
 DI Temecula, CA 92590 USA
 DI 1-909-676-8080
 DI 1-800-437-7500(toll free USA)
 DE P>MAB1984 ;distributor
 RE 1.G>Homo sapiens 1.CN>human 1.SN>vitronectin receptor
 RE 1.a.CC>receptor
 AB Reactant#1 vitronectin receptor alpha subunit syn. for CD61
 SD MAB1984
 LD USA BAL
 EI DA>9107 CV>9108
 CI ;catalog
 SN Synonym>vitronectin receptor
```

```
1012445 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD61
 AN 1012445
 DI P>Cymbus Bioscience Limited
 DI 2 Venture Road
 DI Chilworth Research Center
 DI Southampton, Hampshire SO1 7NS UK
 DI 44-703-767178
 DE C>Thromb/1 ;developer
 DE P>CBL 458 ;discontinued designation
 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD61
 RE 1.a.CC>differentiation
 SD THROMB1
 LD USA BAL
 EI DA>9110 CV>9111
 CI ;catalog
```

```
1013416 RE 1.CE>platelet 1.SN>CD61 1.a.CC>differentiation
 AN 1013416
 DI P>Caltag Laboratories
 DI 1849 Bayshore Blvd. #200
 DI Burlingame, CA 94010
 DI 1-650-652-0468
 DI 1-800-874-4007
 DI 2.P>Medica
 DI 2382 Camino Vida Roble, Suite I
 DI Carlsbad, CA 92009 USA
 DI 1-619-438-1886
 DI 3.P>Sigma Chemical Company
 DI P.O. Box 14508
 DI St. Louis, MO 63178 9916 USA
 DI 1-800-325-3010 (toll free USA)
 DI 1-314-771-5750
 DE C>BL-E6 ;developer
 DE P>BL-E6 ;distributor
 DE P>MHCD6101 ;distributor
 DE P>MHCD6101-4 ;distributor
 DE P>MHCD6115 ;distributor
 DE P>MHCD6115-4 ;distributor
 DE P>MON1051 ;distributor
 DE 2.P>MON1051 ;distributor
 DE 3.P>BL-E6 ;distributor
 DE 3.P>C4321 ;distributor
 DE 3.P>F7902 ;distributor
 DO G>Mus musculus CN>mouse
 PD ;IgG1
 RE 1.CE>platelet 1.SN>CD61 1.a.CC>differentiation
 RE 2.CE>megakaryocyte 2.SN>CD61 2.a.CC>differentiation
 AP ;frozen section
 AV ;biotin conjugate ;fluorescein conjugate
 AV ;3.fluorescein conjugate
 SD BLE6
 SD C4321
 SD F7902
 SD MHCD6101
 SD MHCD61014
 SD MHCD6115
 SD MHCD61154
 SD MON1051
 LD USA BAL
 EI DA>9803
 CI ;catalog
```

```
1013417 RE 1.CE>platelet 1.SN>CD61 1.a.CC>differentiation
 AN 1013417
 DI P>Caltag Laboratories
 DI 1849 Bayshore Blvd. #200
 DI Burlingame, CA 94010
 DI 1-650-652-0468
 DI 1-800-874-4007
 DI 2.P>Medica
 DI 2382 Camino Vida Roble, Suite I
 DI Carlsbad, CA 92009 USA
 DI 1-619-438-1886
 DE C>CRC54 ;developer
 DE P>CRC54 ;distributor
 DE P>MON1147 ;distributor
 DE 2.P>MON1147 ;distributor
 PD ;IgG1
 RE 1.CE>platelet 1.SN>CD61 1.a.CC>differentiation
 RE 2.CE>megakaryocyte 2.SN>CD61 2.a.CC>differentiation
 AP ;frozen section
 SD MON1147
 LD USA BAL
 EI DA>9303
 CI ;catalog
```

```
1014017 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD61
 DI P>Diagast Laboratories
 DI 59, rue de Trevise-B.P. 2034
 DI 59014 Lille Cedex, France
 DI 33-20-52-68-00
 DI DIAGAST (042) 160716F
 DE P>16101V ;distributor
 DE P>16103A ;distributor
 DE P>16105E ;distributor
 PD ;IgG
 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD61
 RE 1.a.CC>differentiation
 AV ;fluorescein conjugate ;phycoerythrin conjugate ;purified
 SD 16101V
 SD 16103A
 SD 16105E
 LD USA BAL
 EI DA>9304
 CI ;catalog
```

1014618 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet 1.SN>CD61
AN 1014618
DI P>BioSource International
DI 820 Flynn Roa
DI Camarillo, CA 93012 USA
DI 1-800-242-0607(toll free USA)
DI 1-805-987-0086
DI 2.P>Cymbus Bioscience Limited
DI 2 Venture Road
DI Chilworth Research Center
DI Southampton, Hampshire SO1 7NS UK
DI 44-703-767178
DI 3.P>Endogen Inc.
DI 30 Commerce Way
DI Woburn, MA 01801-1059 USA
DI 1-781-937-0890
DI 4.P>Genosys Biotechnologies, Inc.
DI 1442 Lake Front Circle, Suite 185
DI The Woodlands, TX 77380-3600 USA
DI 1-713-363-3693
DI 1-800-234-5362 (toll free USA)
DI 5.P>Harlan Bioproducts for Science, Inc.
DI P.O. Box 29176
DI Indianapolis, IN 46229-0176
DI 1-317-894-7536
DI 1-800-9-SCIENCE
DI 6.P>Lampire Biological Laboratories
DI P.O. Box 270
DI Pipersville, PA 18947 USA
DI 1-215-795-2838
DI 7.P>Novocastra Laboratories Ltd.
DI 24 Claremont Place
DI Newcastle upon Tyne NE2 4AA, UK
DI 44-0191 222 8550
DI 8.P>Southern Biotechnology Associates, Inc.
DI P.O. Box 26221
DI Birmingham, AL 35260 USA
DI 1-800-722-2255 (toll free USA)
DI 1-205-945-1774
DI 9.P>T Cell Diagnostics, Inc.
DI 6 Gill Street
DI Woburn, MA 01801-1721 USA
DI 1-800-624-4021
DI 1-617-937-9587
DE C>PM 6/13 ;developer
DE P>AHS6101 ;distributor

```
DE P>AHS6107 ;distributor
DE P>AHS6108 ;distributor
DE P>CS-CD61-CF ;discontinued designation
DE P>CS-CD61-FI ;discontinued designation
DE P>CS-CD61-PE ;discontinued designation
DE 2.P>CBL479 ;distributor
DE 2.P>PM6/13 ;distributor
DE 3.P>MA-6100 ;distributor
DE 3.P>PM6/13 ;distributor
DE 4.P>AM-19-705 ;distributor
DE 4.P>PM6/13 ;distributor
DE 5.P>MCA-728 ;distributor
DE 5.P>MCA-728F ;distributor
DE 5.P>MCA-728PE ;distributor
DE 5.P>PM6/13 ;distributor
DE 6.P>LBL 579 ;distributor
DE 6.P>PM6/13 ;distributor
DE 7.P>NCL-CD61 ;distributor
DE 7.P>PM6/13 ;distributor
DE 8.P>9470-01 ;distributor
DE 8.P>9470-02 ;distributor
DE 8.P>9470-08 ;distributor
DE 8.P>PM6/13 ;distributor
DE 9.P>IA1S09 ;distributor
DE 9.P>PM6/13 ;distributor
DO G>Mus musculus CN>mouse
PD ;IgG1
RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet 1.SN>CD61
RE 1.MW>90 kD 1.a.CC>differentiation
RE 2.G>Homo sapiens 2.CN>human 2.T>plasma 2.SN>CD61
RE 2.MW>90 kD 2.a.CC>differentiation
RE 3.G>Homo sapiens 3.CN>human 3.T>plasma
RE 3.PA>unspecified neoplasm 3.SN>CD61 3.MW>90 kD
RE 3.a.CC>neoplasm 3.b.CC>differentiation
AV ;fluorescein conjugate ;phycoerythrin conjugate ;purified
AV ;3.purified ;5.fluorescein conjugate
AV ;5.phycoerythrin conjugate ;5.purified ;8.biotin conjugate
AV ;8.fluorescein conjugate ;8.purified ;9.purified
SD 947001
SD 947002
SD 947008
SD AHS6101
SD AHS6107
SD AHS6108
SD AM19705
SD CBL479
SD CSCD61CF
```

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SD CSCD61FI
SD CSCD61PE
SD IA1S09
SD LBL579
SD MA6100
SD MCA728
SD MCA728F
SD MCA728PE
SD NCLCD61
SD PM613
LD USA BAL
EI DA>9904
CI ;catalog
```

```
1017042 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet 1.SN>CD61
 AN 1017042
 DI P>Becton Dickinson Immunocytometry Systems
 DI 2350 Qume Drive
 DI San Jose, CA 95131-1807
 DI 1-800-223-8226 (toll free USA)
 DI 1-408-954-2347
 DE P>348090 ;distributor
 DE P>348093 ;distributor
 DE P>559936 ;distributor
 DE P>RUU-PL7F12 ;distributor
 DO G>Mus musculus CN>mouse S>BALB/c
 PD ;IgG1 ;kappa
 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet 1.SN>CD61
 RE 1.a.CC>differentiation 1.b.CC>protein
 AP ;immunofluorescence ;immunoprecipitation
 AV ;fluorescein conjugate ;purified
 SD 348090
 SD 348093
 SD 559936
 SD RUUPL7F12
 LD USA JMJ
 EI DA>9505
 CI ;catalog
```

```
1017635 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD61
 AN 1017635
 DI P>Novocastra Laboratories Ltd.
 DI 24 Claremont Place
 DI Newcastle upon Tyne NE2 4AA, UK
 DI 44-0191 222 8550
 DE P>NCL-CD61 ;distributor
 DE P>PM6/13 ;distributor
 DO G>Mus musculus CN>mouse
 AS ;immunohistochemical staining
 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD61
 RE 1.a.CC>differentiation
 AP ;frozen section
 AV ;ascites
 SD NCLCD61
 SD PM613
 LD USA BAL
 EI DA>9904
 CI ;catalog
```

```
1019745 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD61
 AN 1019745
 DI P>Upstate Biotechnology, Inc.
 DI 199 Saranac Avenue
 DI Lake Placid, NY 12946 USA
 DI 1-617-890-8845
 DI 1-800-233-3991 (toll free USA) (sales)
 DE P>05-275 ;distributor
 DO G>Mus musculus CN>mouse S>BALB/c O>spleen
 PD ;IgG1
 RE 1.G>Homo sapiens 1.CN>human 1.SN>CD61
 RE 1.a.CC>differentiation 1.b.CC>protein
 AP ;immunocytochemistry
 AV ;ascites
 SD 05275
 LD USA JMJ
 EI DA>9611
 CI ;catalog
```

```
1020416 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet 1.SN>CD61
 AN 1020416
 DI P>PanVera Corporation
 DI 545 Science Drive
 DI Madison, WI 53711 USA
 DI 1-800-791-1400
 DI 1-608-233-9450
 DE C>PL8-5 ;distributor
 DE P>TAK M068 ;distributor
 DO G>Mus musculus CN>mouse S>BALB/c O>spleen
 PD ;IgG
 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet 1.SN>CD61
 RE 1.a.CC>differentiation 1.b.CC>protein
 AV ;purified
 SD PL85
 SD TAKM068
 LD USA JMJ
 EI DA>9702
 CI ;catalog
```

```
1020417 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet 1.SN>CD61
 AN 1020417
 DI P>PanVera Corporation
 DI 545 Science Drive
 DI Madison, WI 53711 USA
 DI 1-800-791-1400
 DI 1-608-233-9450
 DE C>PL11-7 ;distributor
 DE P>TAK M069 ;distributor
 DO G>Mus musculus CN>mouse S>BALB/c O>spleen
 PD ;IgG
 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet 1.SN>CD61
 RE 1.a.CC>differentiation 1.b.CC>protein
 AV ;purified
 SD PL117
 SD TAKM069
 LD USA JMJ
 EI DA>9702
 CI ;catalog
```

```
1021005 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet 1.SN>CD61
 AN 1021005
 DI P>Cortex Biochem, Inc.
 DI 1933 Davis Street, Suite 321
 DI San Leandro, CA 94577 USA
 DI 1-800-888-7713 (toll free USA)
 DI 1-510-568-3911(technical)
 DE P>CR1153 ;distributor
 RE 1.G>Homo sapiens 1.CN>human 1.CE>platelet 1.SN>CD61
 RE 1.a.CC>differentiation
 RE 2.G>Homo sapiens 2.CN>human 2.CE>megakaryocyte 2.SN>CD61
 RE 2.a.CC>differentiation
 LD USA CLB
 EI DA>9704
 CI ;catalog
```

```
1011328 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin alpha V
 AN 1011328
 DI P>Chemicon International, Inc.
 DI 28835 Single Oak Dr.
 DI Temecula, CA 92590 USA
 DI 1-909-676-8080
 DI 1-800-437-7500(toll free USA)
 DI 2.P>Life Technologies, Inc.
 DI 8400 Helgerman Ct.
 DI P.O. Box 6009
 DI Gaithersburg, MD 20884-9980 USA
 DI 1-301-840-8000
 DI 1-800-828-6686 (Toll free USA)
 DE P>MAB1958 ;distributor
 DE P>VNR147 ;distributor
 DE 2.P>12084-018 ;distributor
 DE 2.P>VNR147 ;distributor
 PD ;IgG1
 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin alpha V
 RE 1.a.CC>receptor
 AV ;ascites ;2.ascites
 SD 12084018
 SD MAB1958
 SD VNR147
 LD USA BAL
 EI DA>9706 CV>9108
 CI ;catalog
```

```
1011329 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin alpha V
 AN 1011329
 DI P>Chemicon International, Inc.
 DI 28835 Single Oak Dr.
 DI Temecula, CA 92590 USA
 DI 1-909-676-8080
 DI 1-800-437-7500(toll free USA)
 DI 2.P>Life Technologies, Inc.
 DI 8400 Helgerman Ct.
 DI P.O. Box 6009
 DI Gaithersburg, MD 20884-9980 USA
 DI 1-301-840-8000
 DI 1-800-828-6686 (Toll free USA)
 DE P>MAB1960 ;distributor
 DE P>VNR139 ;distributor
 DE 2.P>12085-015 ;distributor
 DE 2.P>VNR139 ;distributor
 PD ;IgG1
 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin alpha V
 RE 1.a.CC>receptor
 AV ;ascites ;2.ascites
 SD 12085015
 SD MAB1960
 SD VNR139
 LD USA BAL
 EI DA>9706 CV>9108
 CI ;catalog
```

```
1011842 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin alpha V
 AN 1011842
 DI P>Biogenesis Ltd.
 DI 7 New Fields
 DI Stinsford Road
 DI Poole BH17 7NF, England
 DI UK
 DI 44-1202 660006
 DE C>1U4/1 ;developer
 DE P>5355-2505 ;distributor
 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin alpha V
 RE 1.a.CC>protein
 AP ;immunoblotting
 AV ;ascites
 SD 1U41
 SD 53552505
 LD USA BAL
 EI DA>9109 CV>9110
 CI ;catalog
```

```
1011843 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin alpha V
 AN 1011843
 DI P>Biogenesis Ltd.
 DI 7 New Fields
 DI Stinsford Road
 DI Poole BH17 7NF, England
 DI UK
 DI 44-1202 660006
 DE C>1U3/0 ;developer
 DE P>5355-2515 ;distributor
 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin alpha V
 RE 1.a.CC>protein
 AP ;immunofluorescence
 AV ;ascites
 SD 1U30
 SD 53552515
 LD USA BAL
 EI DA>9109 CV>9110
 CI ;catalog
```

```
1012705 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin alpha V
 AN 1012705
 DI P>Chemicon International, Inc.
 DI 28835 Single Oak Dr.
 DI Temecula, CA 92590 USA
 DI 1-909-676-8080
 DI 1-800-437-7500(toll free USA)
 DE P>LM142 ;distributor
 DE P>MAB1978 ;distributor
 PD ;IgG
 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin alpha V
 RE 1.a.CC>protein
 AV ;ascites
 SD LM142
 SD MAB1978
 LD USA BAL
 EI DA>9112 CV>9201
 CI ;catalog
```

1013223 RE 1.SN>integrin alpha V 1.a.CC>protein
AN 1013223
DI P>American Qualex International, Inc.
DI 920-A Calle Negocio St.
DI San Clemente, CA 92673
DI 1-714-521-3753
DI 1-800-772-1776 (toll free USA)
DE P>M2580 ;distributor
RE 1.SN>integrin alpha V 1.a.CC>protein
SD M2580
LD USA BAL
EI DA>9204 CV>9204
CI ;catalog

```
1013510 RE 1.G>Homo sapiens 1.CN>human 1.CE>endothelial cell
 AN 1013510
 AU Freed E
 SO EMBO J 1989;8:2955
 DI P>Calbiochem Novabiochem International
 DI P.O. Box 12087
 DI La Jolla, CA 92039-2087
 DI 1-800-854-3417(toll free USA)
 DI 1-619-450-9600
 DE P>407281 ;distributor
 PD ;IgG1
 RE 1.G>Homo sapiens 1.CN>human 1.CE>endothelial cell
 RE 1.SN>integrin alpha V 1.FS>type 1 1.a.CC>protein
 RE 2.G>Homo sapiens 2.CN>human 2.SN>vitronectin
 RE 2.a.CC>protein
 RE 3.G>Homo sapiens 3.CN>human 3.SN>fibrinogen
 RE 3.a.CC>protein
 RE 4.G>Homo sapiens 4.CN>human 4.SN>osteopontin
 RE 4.a.CC>protein
 RE 5.G>Homo sapiens 5.CN>human 5.SN>von Willebrand factor
 RE 5.a.CC>protein
 RE 6.G>Homo sapiens 6.CN>human 6.O>bone 6.SN>sialoprotein I
 RE 6.a.CC>protein
 AP ;ELISA ;immunofluorescence ;immunoprecipitation
 AV ;ascites ;lyophilized
 SD 407281
 LD USA BAL
 EI DA>9303
 CI ;catalog
 SN Synonym>fibrinogen
 SN Synonym>von Willebrand factor
```

```
1013511 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin alpha V
 AN 1013511
 DI P>Calbiochem Novabiochem International
 DI P.O. Box 12087
 DI La Jolla, CA 92039-2087
 DI 1-800-854-3417(toll free USA)
 DI 1-619-450-9600
 DE P>407282 ;distributor
 PD ;IgG1
 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin alpha V
 RE 1.FS>type 2 1.a.CC>protein
 RE 2.G>Homo sapiens 2.CN>human 2.SN>vitronectin
 RE 2.a.CC>protein
 RE 3.G>Homo sapiens 3.CN>human 3.SN>fibrinogen
 RE 3.a.CC>protein
 RE 4.G>Homo sapiens 4.CN>human 4.SN>osteopontin
 RE 4.a.CC>protein
 RE 5.G>Homo sapiens 5.CN>human 5.SN>von Willebrand factor
 RE 5.a.CC>protein
 RE 6.G>Homo sapiens 6.CN>human 6.O>bone 6.SN>sialoprotein I
 RE 6.a.CC>protein
 AP ;ELISA ;immunoblotting
 AV ;ascites ;lyophilized
 SD 407282
 LD USA BAL
 EI DA>9303
 CI ;catalog
 SN Synonym>fibrinogen
 SN Synonym>von Willebrand factor
```

1014225 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin alpha V beta 5
AN 1014225
AU Wayner EA
SO J Cell Biol 1991;113:919
DI P>Becton Dickinson Immunocytometry Systems
DI 2350 Qume Drive
DI San Jose, CA 95131-1807
DI 1-800-223-8226 (toll free USA)
DI 1-408-954-2347
DI 2.P>Chemicon International, Inc.
DI 28835 Single Oak Dr.
DI Temecula, CA 92590 USA
DI 1-909-676-8080
DI 1-800-437-7500(toll free USA)
DI 3.P>Life Technologies, Inc.
DI 8400 Helgerman Ct.
DI P.O. Box 6009
DI Gaithersburg, MD 20884-9980 USA
DI 1-301-840-8000
DI 1-800-828-6686 (Toll free USA)
DI 4.P>Telios Pharmaceuticals, Inc.
DI 4757 Nexus Centre Drive
DI San Diego, CA 92121 USA
DI 1-619-622-2650
DE C>P1F6 ;developer
DE P>550045 ;distributor
DE P>P1F6 ;distributor
DE 2.P>MAB1961 ;distributor
DE 2.P>P1F6 ;distributor
DE 3.P>12078-010 ;distributor
DE 3.P>P1F6 ;distributor
DE 4.P>A035 ;distributor
DO G>Mus musculus CN>mouse
PD ;IgG1
RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin alpha V beta 5
RE 1.a.CC>receptor
AP ;immunofluorescence ;immunoprecipitation
AV ;2.ascites ;3.ascites ;4.ascites
SD 12078010
SD 550045
SD A035
SD MAB1961
SD P1F6
LD USA BAL
EI DA>9706
CI ;catalog

```
1014277 RE 1.G>Homo sapiens 1.CN>human 1.CE>endothelial cell
 AN 1014277
 DI P>Bio-Science Products AG
 DI Gerliswilstrasse 43
 DI Postfach 1173
 DI CH-6020 Emmenbrucke, Switzerland
 DI 41-555875
 DE P>0121005 ;distributor
 RE 1.G>Homo sapiens 1.CN>human 1.CE>endothelial cell
 RE 1.SN>integrin alpha V 1.a.CC>receptor
 RE 2.G>Homo sapiens 2.CN>human 2.PA>carcinoma
 RE 2.SN>integrin alpha V 2.a.CC>neoplasm 2.b.CC>receptor
 NR 1.G>Homo sapiens 1.CN>human 1.SN>fibronectin receptor
 NR 1.a.CC>receptor
 NR 2.G>Homo sapiens 2.CN>human 2.SN>CD41
 NR 2.a.CC>differentiation
 AP ;ELISA ;immunofluorescence ;not immunoblotting
 AP ;immunoprecipitation
 LD USA BAL
 EI DA>9305
 CI ;catalog
 SN Synonym>CD41 1014277 SN Synonym>CD41
 SN Synonym>fibronectin receptor
```

1014278 RE 1.G>Homo sapiens 1.CN>human 1.CE>endothelial cell
AN 1014278
DI P>Bio-Science Products AG
DI Gerliswilstrasse 43
DI Postfach 1173
DI CH-6020 Emmenbrucke, Switzerland
DI 41-555875
DE P>0121006 ;distributor
AS ;immunoblot
RE 1.G>Homo sapiens 1.CN>human 1.CE>endothelial cell
RE 1.SN>integrin alpha V 1.a.CC>receptor
RE 2.G>Homo sapiens 2.CN>human 2.PA>carcinoma
RE 2.SN>integrin alpha V 2.a.CC>neoplasm 2.b.CC>receptor
AP ;immunoassay
LD USA BAL
EI DA>9305
CI ;catalog

1023559 RE 1.G>Mus musculus 1.CN>mouse 1.SN>integrin alpha V
SO Biochemistry 1990;29:10191
SO Exp Cell Res 1993;205:25
DI P>Upstate Biotechnology, Inc.
DI 199 Saranac Avenue
DI Lake Placid, NY 12946 USA
DI 1-617-890-8845
DI 1-800-233-3991 (toll free USA) (sales)
DE P>05-437 ;distributor
DO G>Mus musculus CN>mouse
RE 1.G>Mus musculus 1.CN>mouse 1.SN>integrin alpha V
RE 1.MW>160 kD 1.a.CC>differentiation 1.b.CC>receptor
AP ;Western blot ;immunoprecipitation ;immunohistochemistry
AV ;ascites
AB Reactant is also known as vitronectin receptor alpha subunit and CD51.
SD 05437
LD USA MCM
EI DA>9807
CI ;catalog

1023927 RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin alpha V
AN 1023927
SO J Biol Chem 1994;269:6940
DI P>Chemicon International, Inc.
DI 28835 Single Oak Dr.
DI Temecula, CA 92590 USA
DI 1-909-676-8080
DI 1-800-437-7500 (toll free USA)
DE C>P3G8 ;distributor
IM G>Homo sapiens CN>human O>lung PA>carcinoma a.CC>neoplasm
DO G.Mus musculus CN>mouse
PD ;IgG1
RE 1.G>Homo sapiens 1.CN>human 1.SN>integrin alpha V
RE 1.a.CC>differentiation 1.b.CC>receptor
AP ;immunocytology ;immunohistochemistry ;immunoprecipitation
AP ;flow cytometry ;ELISA ;FACS
AV ;purified
AB Reactant is also known as CD51 and vitronectin receptor alpha subunit.
AB Product reacts with all alpha V-containing integrin receptors.
AB Product will react with some lymphoid cell lines (B cells), many
AB carcinoma and melanoma cell lines and osteosarcomas.
SD MAB1953
SD P3G8
LD USA MCM
EI DA>9808
CI ;catalog

CLAIMS:

1. A method of treating mammalian dendritic cells in vitro to induce immune tolerance therein which comprises exposing said cells to an agonist of the cell surface receptors CD36 and/or CD51 as expressed on mammalian dendritic cells.

2. A method as claimed in claim 1 wherein said dendritic cells are human or mouse.

3. A method as claimed in claim 1 or 2 wherein said agonist is a molecule identified as such by any one of the methods of claims 15 to 32.

4. A method as claimed in claim 1 or 2 wherein said agonist is selected from: an antibody with an affinity for an epitope of CD36, an antibody with an affinity for an epitope of CD51, the Plasmodium falciparum protein pf-EMP-1, a protein comprising the active binding domain of pf-EMP-1, thrombospondin, apoptotic cells or a negatively charged phospholipid.

5. A method as claimed in claim 1 or 2 which comprises exposing said dendritic cells to two or more of the agonists of claim 4.

6. A method as claimed in claim 4 or claim 5 wherein the CD36 agonist any one of the antibodies listed in Appendix 1.

7. A method as claimed in claim 4 or claim 5 wherein the CD51 agonist is any one of the antibodies listed in Appendix 2.

8. A method as claimed in claim 4 or claim 5

wherein the pf-EMP-1 active binding domain comprises the amino acid sequence shown in Figure 2.

9. A method as claimed in any one of claims 40 to 47 wherein said cells are exposed to an antigenic material.

10. A method as claimed in claim 9 wherein said antigenic material is an auto-antigen associated with a particular auto-immune disease.

11. A method as claimed in claim 9 or 10 wherein the cells so produced are subsequently matured by exposure to an immune stimulus.

12. A method as claimed in any of claims 1 to 11 wherein said dendritic cells are prepared from human peripheral blood and or derived from CD34+ stem cells or monocytes.

13. A dendritic cell preparation obtainable by the method of any of claims 1 to 12 for use as a medicament.

14. A dendritic cell preparation obtainable by the method of any of claims 1 to 12 for use in inducing peripheral immune tolerance in a human.

15. A method of identifying a molecule which is an agonist of cell surface receptor CD36 and/or CD51 as expressed by mammalian dendritic cells which method comprises:

a) exposing immature mammalian dendritic cells to the molecule to be tested,

b) exposing said immature dendritic cells to an immune stimulus and

c) determining the degree of maturation manifested by said dendritic cells,

wherein impaired maturation in response to the immune stimulus is an indication that said molecule under test is a CD36 and/or CD51 agonist.

16. A method as claimed in claim 15 wherein said dendritic cells are human cells or mouse cells.

17. A method as claimed in claim 15 or 16 wherein maturation of said dendritic cells is determined by examining the antigen-presenting ability of said cells.

18. A method as claimed in any of claims 15 to 17 wherein maturation of said dendritic cells is determined by examining said cells for expression of at least one cell surface antigen whose level of expression is enhanced in response to an immune stimulus.

19. A method as claimed in claim 18 wherein maturation of said dendritic cells is determined by measuring the level of expression of one or more of the following panel of antigens:
HLA DR, CD54, CD40, CD83 and CD86.

20. A method as claimed in claim 19 wherein said cells are also examined for expression of CD80.

21. A method as claimed in any one of claims 18 to 20 wherein the level of expression of said antigens is detected using a labelled antibody.

22. A method as claimed in 15 or 16 wherein maturation of said dendritic cells is determined by measuring said cells' ability to induce T-cell

proliferation.

23. The method of claim 15 or 16 wherein maturation of said dendritic cells is determined by quantifying the level of cytokines secreted from said cells.

24. The method of claim 23 wherein the level of secretion TNFα, IL12P70 and IL10 is measured.

25. A method as claimed in any one of claims 15 to 24 wherein said immune stimulus is lipopolysaccharide, TNFα, CD40L or monocyte conditioned medium (MCM).

26. A method as claimed in any one of claims 15 to 25 wherein if said test molecule is found to be a potential agonist of CD36 and/or CD51 the method further comprises the step of exposing said molecule to a purified sample of CD36 and/or CD51 and detecting any direct binding between said molecule and CD36 and/or CD51.

27. A method as claimed in claim 26 wherein said purified CD36 or CD51 is immobilised to a solid surface.

28. A method as claimed in claim 26 or claim 27 wherein said molecule is labelled with a detectable label.

29. A method as claimed in any of claims 26 to 28 which further comprises the step of exposing said molecule to a purified sample of $\alpha_v\beta_3$ or $\alpha_v\beta_5$ and detecting any direct binding between said molecule and said $\alpha_v\beta_3$ or $\alpha_v\beta_5$.

30. A method as claimed in any one of claims 26 to 29 which further comprises the step of exposing said molecule to a purified sample of thrombospondin and detecting any direct binding between said molecule and thrombospondin.

31. A method as claimed in claim 29 or claim 30 wherein said molecule is labelled with a detectable label.

32. A method as claimed in any of claims 29 to 31 wherein said $\alpha_v\beta_3$, $\alpha_v\beta_5$ or thrombospondin is immobilised to a solid surface.

33. A pharmaceutical composition suitable for inducing peripheral immune tolerance in a mammal which comprises an agonist of the cell surface receptor CD36 as expressed on mammalian dendritic cells and a pharmacologically acceptable carrier or diluent.

34. A composition as claimed in claim 33 which is suitable for inducing peripheral immune tolerance in a human wherein said CD36 agonist is selected from: an antibody with an affinity for an epitope of CD36, the Plasmodium falciparum protein pf-EMP-1, a protein comprising the active binding domain of pf-EMP-1 for CD36 and/or thrombospondin, thrombospondin, apoptotic cells or a negatively-charged phospholipid.

35. A composition as claimed in claim 20 wherein said CD36 agonist is any one of the antibodies listed in Appendix 1.

36. A composition as claimed in claim 20 wherein the pf-EMP-1 active binding domain comprises the amino acid sequence as shown in Figure 2.

37. A composition as claimed in claim 19 wherein said CD36 agonist is a molecule identified as such by any one of the methods of claims 15 to 32.

38. An agonist of the cell surface receptor CD36 as expressed on mammalian dendritic cells for use as a medicament.

39. An agonist for use as claimed in claim 38 wherein said medicament is used to induce a state of immune tolerance in a human.

40. An agonist for use as claimed in claim 38 or 39 which is suitable for treating a human and wherein said CD36 agonist is selected from: an antibody with an affinity for an epitope of CD36, the Plasmodium falciparum protein pf-EMP-1, a protein comprising the active binding domain of pf-EMP-1 for CD36 or thrombospondin, thrombospondin, apoptotic cells or a negatively charged phospholipid.

41. An agonist for use as claimed in claim 40 wherein said CD36 agonist is any one of the antibodies listed in Appendix 1.

42. An agonist for use as claimed in claim 40 wherein the pf-EMP-1 active binding domain comprises the amino acid sequence as shown in Figure 2.

43. A pharmaceutical composition suitable for inducing peripheral immune tolerance in a mammal which comprises an agonist of the cell surface receptor CD51 as expressed by mammalian dendritic cells and a pharmacologically acceptable carrier or diluent.

44. A composition as claimed in claim 43 suitable for inducing immune tolerance in a human

wherein said CD51 agonist is selected from: an antibody with an affinity for an epitope of CD51, thrombospondin, apoptotic cells or a negatively charged phospholipid.

45. A composition as claimed in claim 44 wherein said CD51 agonist is any one of the antibodies listed in Appendix 2.

46. A composition as claimed in claim 43 or 44 which comprises the Plasmodium falciparum protein pf-EMP-1 or a protein comprising an active binding domain thereof and thrombospondin.

47. A composition as claimed in claim 46 wherein said active binding domain of pf-EMP-1 comprises the amino acid sequence shown in Figure 2.

48. A composition as claimed in claim 43 wherein said CD51 agonist is a molecule identified as such by any one of the methods of claims 15 to 32.

49. An agonist of the cell surface receptor CD51 as expressed on mammalian dendritic cells for use as a medicament.

50. An agonist for use as claimed in claim 49 wherein said medicament is used to induce a state of immune tolerance in a human.

51. An agonist for use as claimed in claim 49 or 50 which is suitable for administration to a human wherein said CD 51 agonist is selected from: an antibody with an affinity for an epitope of CD51, thrombospondin, apoptotic cells or a negatively charged phospholipid.

52. An agonist for use as claimed in claim 51 wherein said CD51 agonist is any one of the antibodies listed in Appendix 2.

53. An agonist for use as claimed in claim 49 which is suitable for administration to a human and which comprises, in combination, the Plasmodium falciparum protein pf-EMP-1 or a protein comprising an active binding domain thereof and thrombospondin.

54. Use of a method comprising the following steps for identifying a molecule capable of preventing the adherence of red blood cells infected with a malarial parasite to human dendritic cells:

a) exposing a purified preparation of the human cell surface receptor CD36 to:-

I) the molecule to be tested and

ii) parasitised human red blood cells,

either consecutively or simultaneously and

b) determining the level of adherence of said parasitised red blood cells to CD36

wherein a reduction in the level of adherence in the presence of the test molecule compared to the level in the absence of said molecule is an indication that said molecule is capable of preventing the adherence of red blood cells infected with the malarial parasite to human dendritic cells.

55. Use of a method comprising the following steps for identifying a molecule capable of preventing the adherence of red blood cells infected with the malarial parasite to human dendritic cells:

a) exposing a purified preparation of human thrombospondin to:

I) the molecule to be tested and

ii) parasitised human red blood cells,

either consecutively or simultaneously and

b) determining the level of adherence of said parasitised red blood cells to thrombospondin,

wherein a reduction in the level of adherence to thrombospondin in the presence of the test molecule compared to the level in the absence of said molecule is an indication that said molecule is capable of preventing the adherence of red blood cells infected with the malarial parasite to human dendritic cells.

56. Use of a method as claimed in claim 54 or claim 55 wherein said red blood cells are infected with Plasmodium falciparum.

57. Use of a method as claimed in claim 56 wherein the Plasmodium falciparum strain is ITO/A4, ITO/C24 or MC.

58. Use of a method as claimed in claim 54 wherein said CD36 is immobilised on a solid surface.

59. Use of a method as claimed in claim 55 wherein said thrombospondin is immobilised on a solid surface.

60. Use of a method as claimed in claim 58 or claim 59 wherein the level of adherence of said parasitised red blood cells to CD36 or thrombospondin is determined by the additional steps of:

a) washing the immobilised CD36 or thrombospondin to remove non-adhered red blood cells and

b) applying a stain to said immobilised CD36 or thrombospondin which is specific for parasitised or non-parasitised red blood cells.

61. Use of a method as claimed in claim 60 wherein said stain is detectable by eye, by microscopy or by a spectrophotometric method.

62. Use of a method as claimed in claim 54 which comprises applying simultaneously or consecutively the method of claim 55.

63. A method of identifying a molecule capable of preventing the adherence of red blood cells infected with a malarial parasite to human dendritic cells which comprises:

a) exposing immature human dendritic cells to the Plasmodium falciparum protein pf-EMP-1 or an active binding domain thereof in the presence or absence of the molecule to be tested,

b) exposing said immature dendritic cells to an immune stimulus and

c) determining the degree of maturation manifested by said dendritic cells,

wherein any maturation of said dendritic cells in the presence of the test molecule over and above that manifested in the absence of said molecule is an indication that said molecule is capable of preventing adherence of red blood cells infected with a malarial parasite to human dendritic cells.

64. A method as claimed in claim 63 wherein maturation of said dendritic cells is determined by examining the antigen-presenting ability of said cells.

65. A method as claimed in claim 63 or claim 64 wherein maturation of said dendritic cells is determined by examining said cells for expression of at least one cell surface antigen whose expression level is enhanced in response to an immune stimulus.

66. A method as claimed in claim 65 wherein maturation of said dendritic cells is determined by

measuring the level of expression of two or more of the following panel of antigens:
HLA DR, CD54, CD40, CD83 and CD86.

67. A method as claimed in claim 66 wherein said cells are also examined for expression of CD80.

68. A method as claimed in any one of claims 65 to 67 wherein the level of expression of said antigen is detected using a labelled antibody.

69. A method as claimed in claim 63 wherein maturation is determined by measuring said cells' ability to induce T-cell proliferation.

70. A method as claimed in claim 63 wherein maturation of said dendritic cells is determined by quantifying the level of cytokines secreted from said cells.

71. A method as claimed in claim 70 wherein the level of secretion of TNFα, IL12P70 and IL10 is measured.

72. A method as claimed in any one of claims 63 to 71 wherein said immune stimulus is lipopolysaccharide, TNF alpha, CD40L or monocyte conditioned medium (MCM).

73. A pharmaceutical composition useful for the treatment of malaria which comprises a molecule capable of preventing the adherence of red blood cells infected with the malarial parasite to human dendritic cells which has been identified by the method of any one of claims 63 to 72 and a pharmacologically acceptable carrier or diluent.

74. A molecule identified as being capable of preventing the adherence of red blood cells infected with the malarial parasite to human dendritic cells by the method of any one of claims 63 to 72 for use in the treatment of malaria.

75. A pharmaceutical composition useful for the treatment of malaria which comprises a molecule capable of preventing the adherence of red blood cells infected with the malarial parasite to human dendritic cells which has been identified by the use of the method of any one of claims 54 to 62.

76. A molecule identified as being capable of preventing the adherence of red blood cells infected with the malarial parasite to human dendritic cells by use of the method as claimed in any one of claims 54 to 62.

77. A method of identifying a molecule which is an agonist of cell surface receptors CD36 and/or CD51 and/or a receptor for thrombospondin as expressed on antigen-presenting cells of the mammalian immune system which method comprises:

a) exposing mammalian antigen-presenting cells to the molecule to be tested,

b) exposing said cells to an immune stimulus and

c) determining the response to said immune stimulus by said cells,

wherein an impaired response compared to the response in the absence of said test molecule is an indication that said molecule under test is a agonist of CD36 and/or CD51 and/or a thrombospondin receptor.

78. A method as claimed in claim 77 wherein said thrombospondin receptor is not CD47.

79. A method as claimed in claim 77 or claim 78 wherein said response is maturation of said antigen-presenting cell.

80. A method as claimed in any one of claims 77 to 79 wherein said antigen-presenting cell of the immune system is selected from a dendritic cell, a macrophage, a B-lymphocyte or a monocyte.

81. A method as claimed in any of claims 77 to 80 which includes the features of any of claims 16 to 18 or 21 to 32.

82. A method of treating mammalian antigen-presenting cells in vitro to induce immune tolerance therein which comprises exposing said cells to an agonist of the cell surface receptor for thrombospondin and/or an agonist for the cell surface receptors CD36 and/or CD51.

83. A method as claimed in claim 82 wherein said antigen-presenting cell is human or mouse.

84. A method as claimed in claim 82 or 83 wherein said antigen presenting cell is selected from a dendritic cell, a macrophage, a B-lymphocyte or a monocyte.

85. A method as claimed in any one of claims 82 to 84 wherein said agonist is a molecule identified as such by the method of any one of claims 77 to 81.

86. A method as claimed in any one of claims 82 to 85 which includes the features of any one of claims 4 to 12.

87. A method as claimed in any one of claims 82 to 85 wherein said antigen-presenting cells are exposed to an antibody to an epitope of a thrombospondin receptor.

88. A method as claimed in claim 87 wherein said agonist is any one of the antibodies listed in Appendix 3.

89. A method as claimed in claim 87 or claim 88, which includes the features of any of claims 9 to 12.

90. An antigen-presenting cell preparation obtainable by the method of any one of claims 82 to 89 for use as a medicament.

91. As antigen-presenting cell preparation obtainable by the method of any one of claims 82 to 89 for use in inducing peripheral immune tolerance in a human.

92. A method of identifying a molecule which is an agonist of a β-integrin associated with the cell surface receptor CD51 as expressed on antigen-presenting cells of the mammalian immune system which method comprises:

a) exposing mammalian antigen-presenting cells to the molecule to be tested,

b) exposing said cells to an immune stimulus and

c) determining the response to said immune stimulus by said cells,

wherein an impaired response compared to the response in the absence of said test molecule is an indication that said molecule is an agonist of a β-integrin associated with the cell surface receptor CD51.

93. A method as claimed in claim 92 which includes the features of claim 78 or claim 79

94. A method as claimed in claim 92 to 93 which further includes the features of any one of claims 16 to 25 or 29 to 32.

95. A method as claimed in any one of claims 92 to 94 wherein said β-integrin is β3 or β5.

96. A pharmaceutical composition suitable for inducing peripheral immune tolerance in a mammal which comprises an agonist of a β-integrin associated with the cell surface receptor CD51 as expressed on mammalian antigen-presenting cells and a pharmacologically acceptable carrier or diluent.

97. A pharmaceutical composition as claimed in claim 96 wherein the β-integrin is β3 or β5.

98. A method of inducing a state of immune tolerance in antigen-presenting cells of the mammalian immune system which comprises exposing said cells *ex-vivo* to an agonist of a β-integrin.

99. A method as claimed in claim 97 wherein said β-integrin is β3 or β5.

100. A method as claimed in claim 97 to 98 wherein said antigen presenting cells are human.

101. A method as claimed in claim 97 or 99 wherein said cells are exposed to an antigenic material.

102. A preparation of cells obtainable by the method as claimed in any one of claims 97 to 100 for

use as a medicament.

103. A preparation of cells obtainable by the method as claimed in any one of claims 97 to 100 for use in inducing immune-tolerance in a human.

104. A pharmaceutical composition suitable for inducing peripheral immune tolerance in a mammal which comprises an agonist of a thrombospondin receptor and a pharmacologically acceptable carrier or diluent.

105. A composition as claimed in claim 104 wherein said thrombospondin receptor is not CD47.

106. A preparation of apoptotic cells for use in inducing peripheral immune tolerance in a mammal.

107. A preparation as claimed in claim 106 wherein said mammal is a human.

108. A preparation comprising a negatively charged phospholipid for use in inducing peripheral immune tolerance in a mammal.

109. A preparation as claimed in claim 108 wherein said mammal is a human.

110. A preparation as claimed in claim 108 or 109 which comprises liposomes including a negatively charged phospholipid.

111. A preparation as claimed any one of claims 108 to 110 wherein said negatively charged phospholipid is phosphatidylserine.

112. A method of inducing a state of immune tolerance in antigen-presenting cells of the mammalian

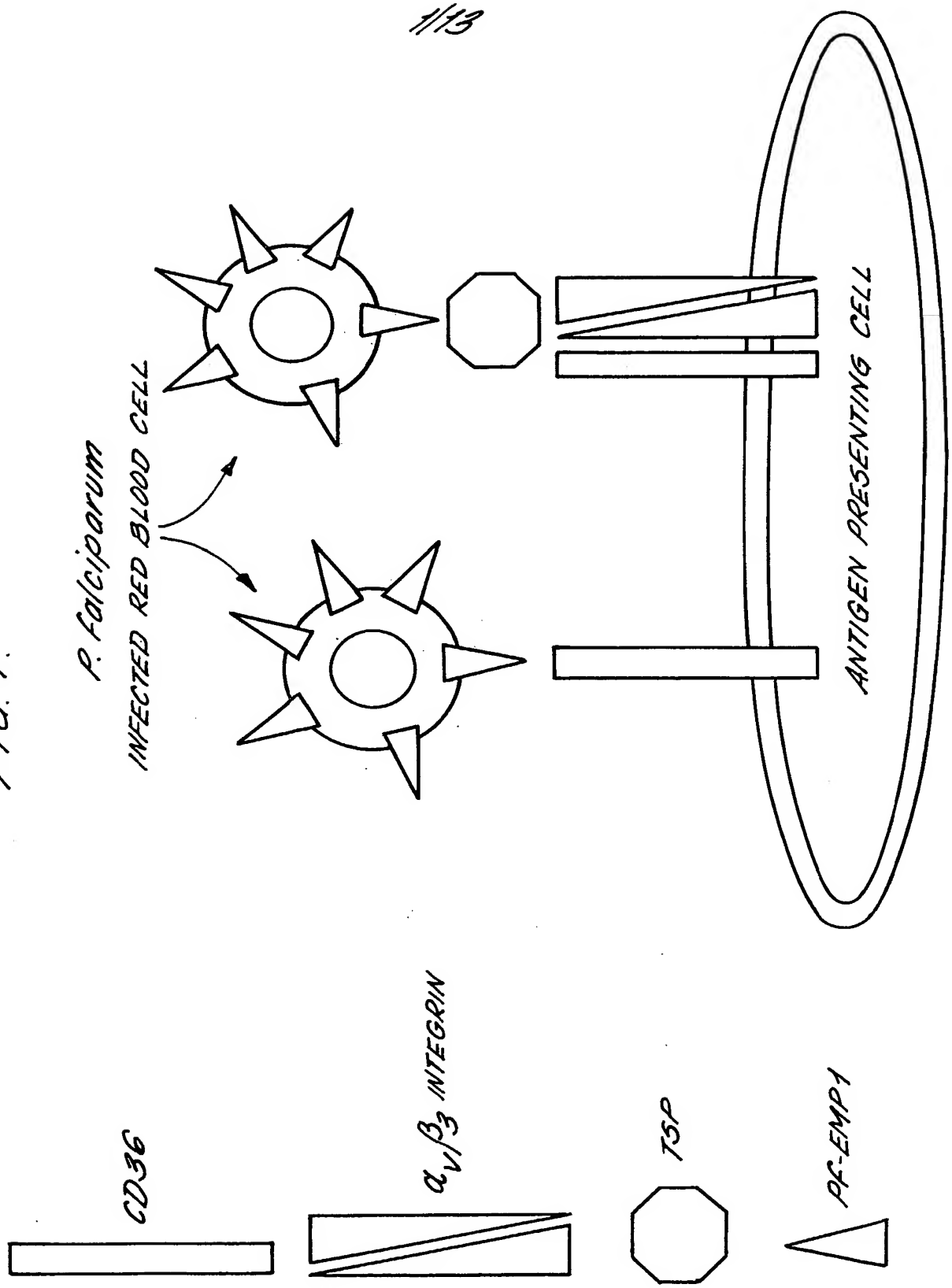
immune system which comprises exposing said cells *ex-vivo* to a composition or preparation as claimed in any one of claims 104 to 111.

113. A method as claimed in claim 112 wherein said cells are exposed to an antigenic material.

114. A preparation of antigen-presenting cells obtainable by the method of claims 112 or 113.

115. A method of treating a human to induce peripheral immune tolerance therein comprising administering to said human a substance selected from the group consisting of: an agonist of CD36, an agonist of CD51, an agonist of a thrombospondin receptor, an agonist of a β-integrin and a preparation of cells of any of claims 13, 14, 90, 91,102 or 114.

FIG. 1.


P. falciparum
INFECTED RED BLOOD CELL
ANTIGEN PRESENTING CELL
CD36
$\alpha_V\beta_3$ INTEGRIN
TSP
PF-EMP1

2/43

FIG. 2.

AMINO ACID SEQUENCE OF THE CIDR FRAGMENT OF THE A4-VAR GENE (COMPLETE SEQUENCE ACCESSION NO L42244)

402- TDEIKKNDD TTITTEYGTI NNMYRKDFYK HLEEKYKTVD

AFLNLLNKEK ECKNHPEVGE GKKKYIDFND NIETFSHTEY

REPCPWCGIE EQKDGKWKRI NDHSACKEEE LYTPKENAKY

TKINVLTSGE GHEDIAKRLK EFCTKTQNGG GGSDDCGGNS

DSSLCEPWQC YQPDQLEKVG GGEVDDKLKG AGGLCIFEKM

KGEKKVKKQK TFNNFFNFWV AHVLKDSIDW RTQLTKCLSE

DKLKKCEKGC KSNCECFKKW IEKKEKEWIK VKDQFNKQTD

FLEWKHYLVL ETILENYYFE NIQKAYGDLK SIQEMKKMIK

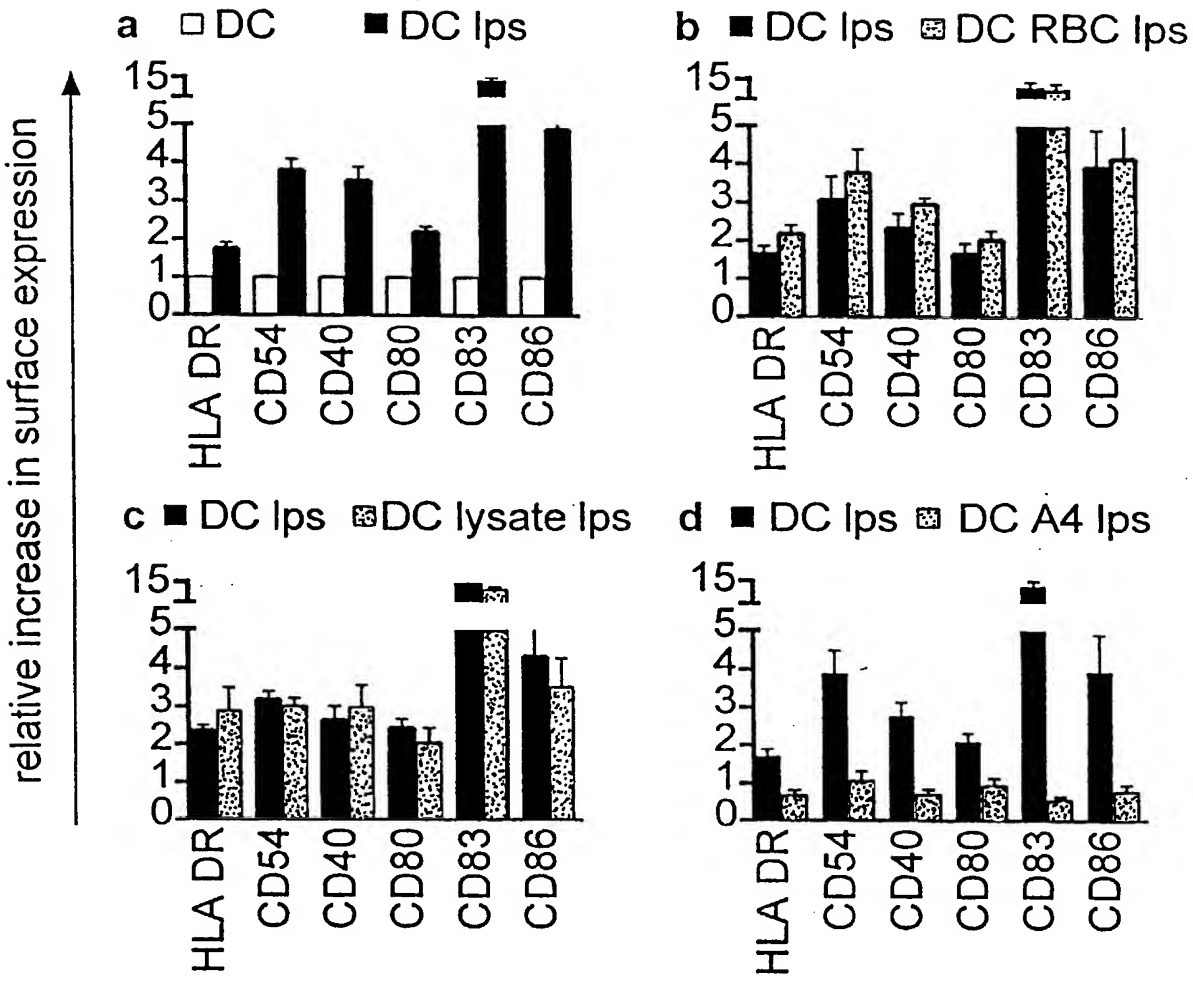
ENKQNKNRTK DDEDALDVLF DHEKEEAEDC LDIHEDDDDD

DECVEEIEKI PNNPCSGTRH RAMVKNVAAD MYRAARQQLR

NRAGGRKTLR ADASQGHYNG KANESVLKDV CDITNQYSNA

IGDSKD -846

FIG. 3.


a DC DC Ips
b DC Ips DC RBC Ips
c DC Ips DC lysate Ips
d DC Ips DC A4 Ips
relative increase in surface expression
0
1
2
3
4
5
15
HLA DR
CD54
CD40
CD80
CD83
CD86

4/13

FIG. 4.

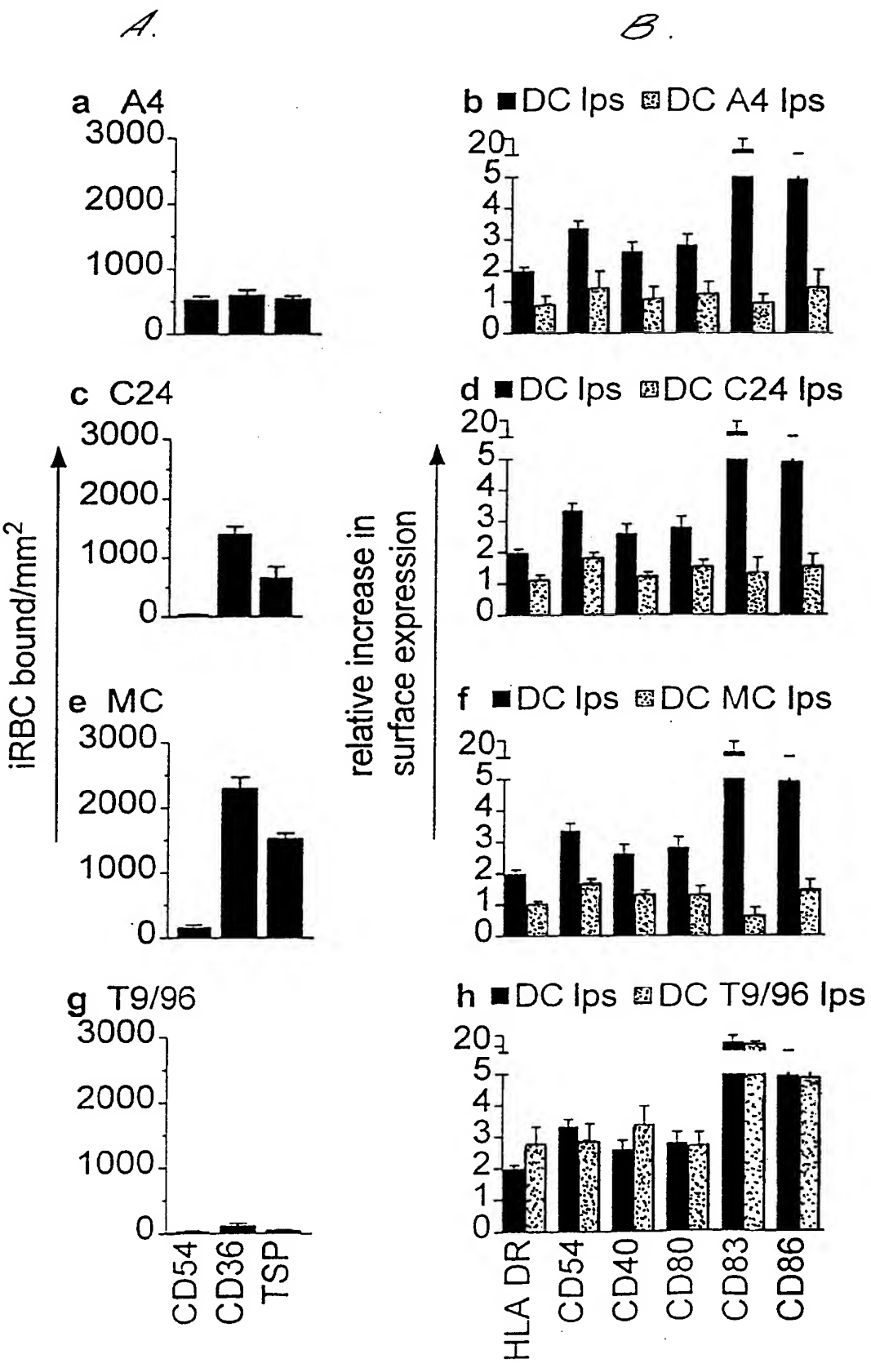

A.
B.
a A4
b DC Ips DC A4 Ips
c C24
d DC Ips DC C24 Ips
e MC
f DC Ips DC MC Ips
g T9/96
h DC Ips DC T9/96 Ips
iRBC bound/mm2
relative increase in surface expression
3000
2000
1000
0
20
5
4
3
2
1
0
CD54
CD36
TSP
HLA DR
CD54
CD40
CD80
CD83
CD86

FIG. 5.

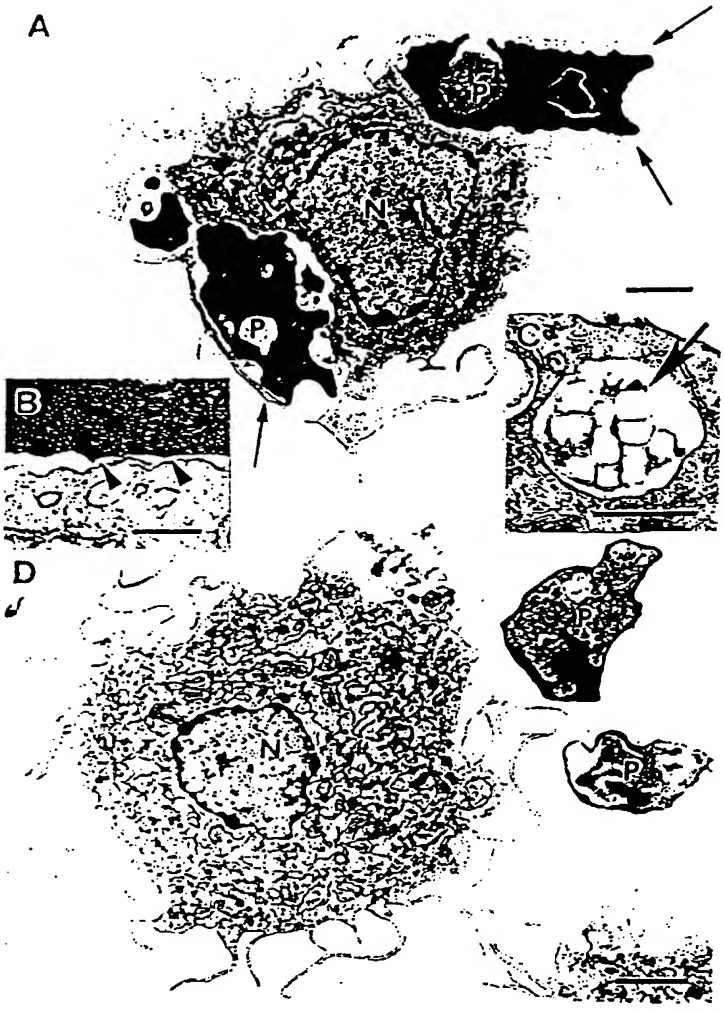


FIG. 6.

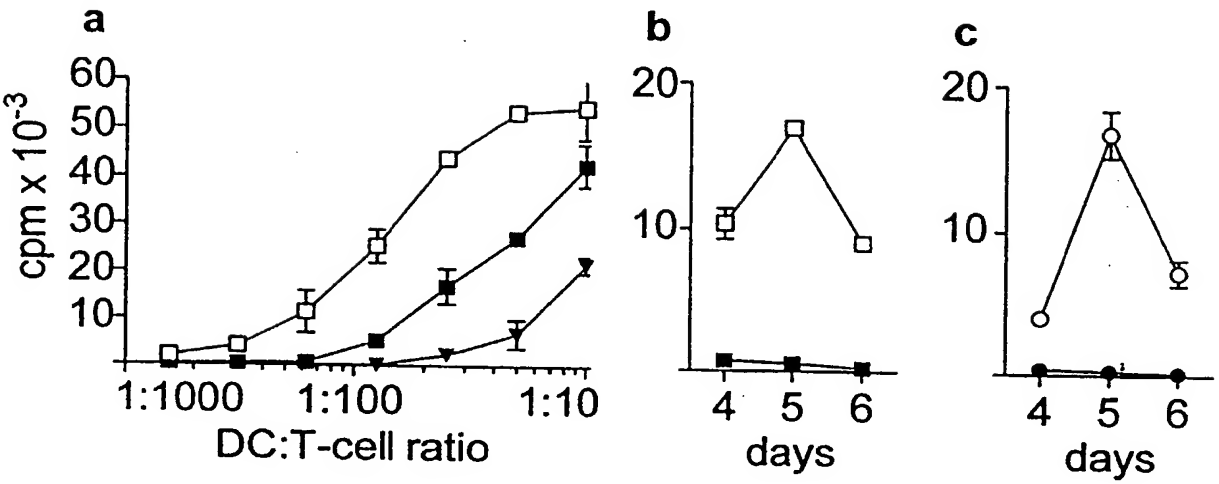

a
b
c
cpm x 10-3
60
50
40
30
20
10
1:1000
1:100
1:10
DC:T-cell ratio
20
10
4
5
6
days
20
10
4
5
6
days

FIG. 7.

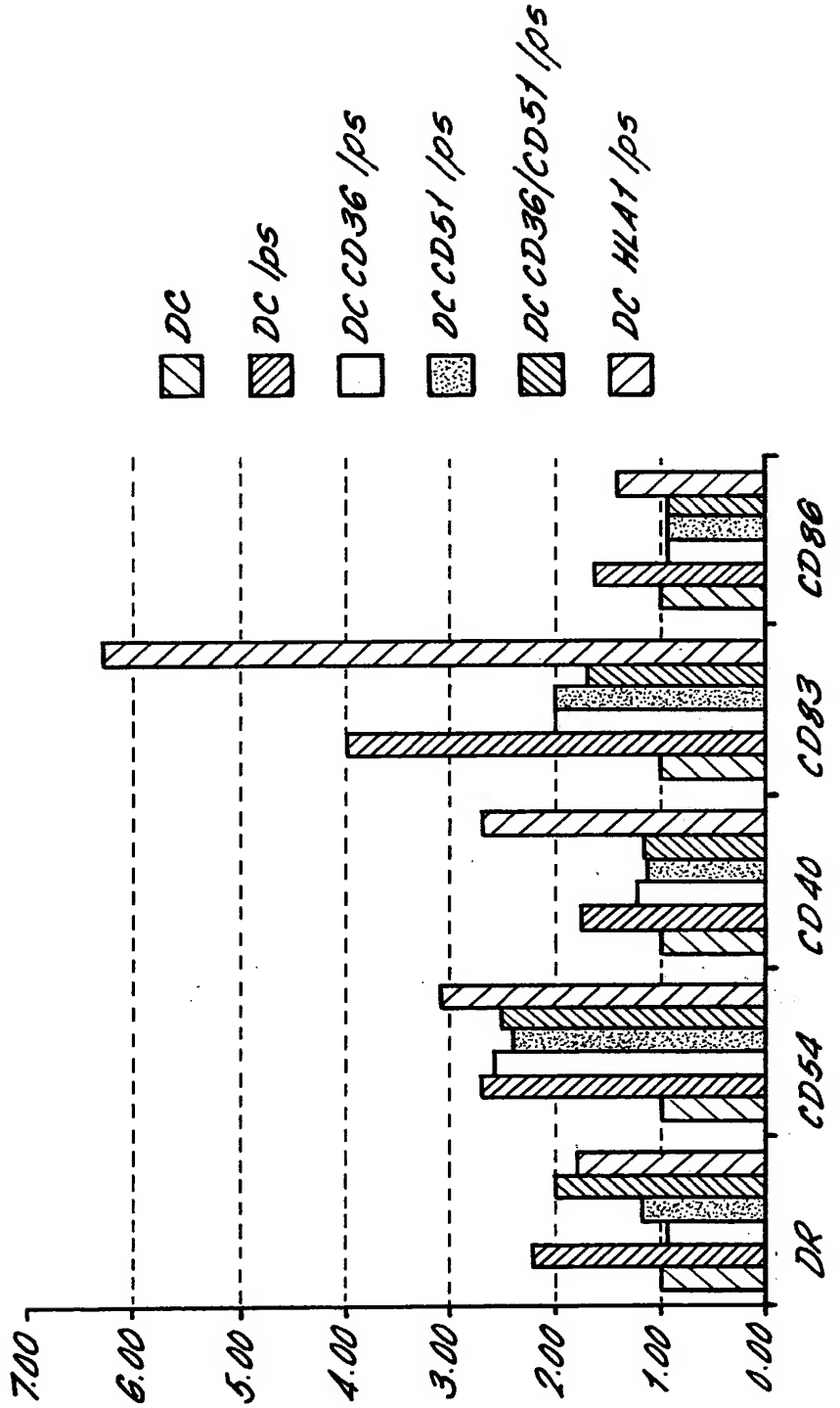
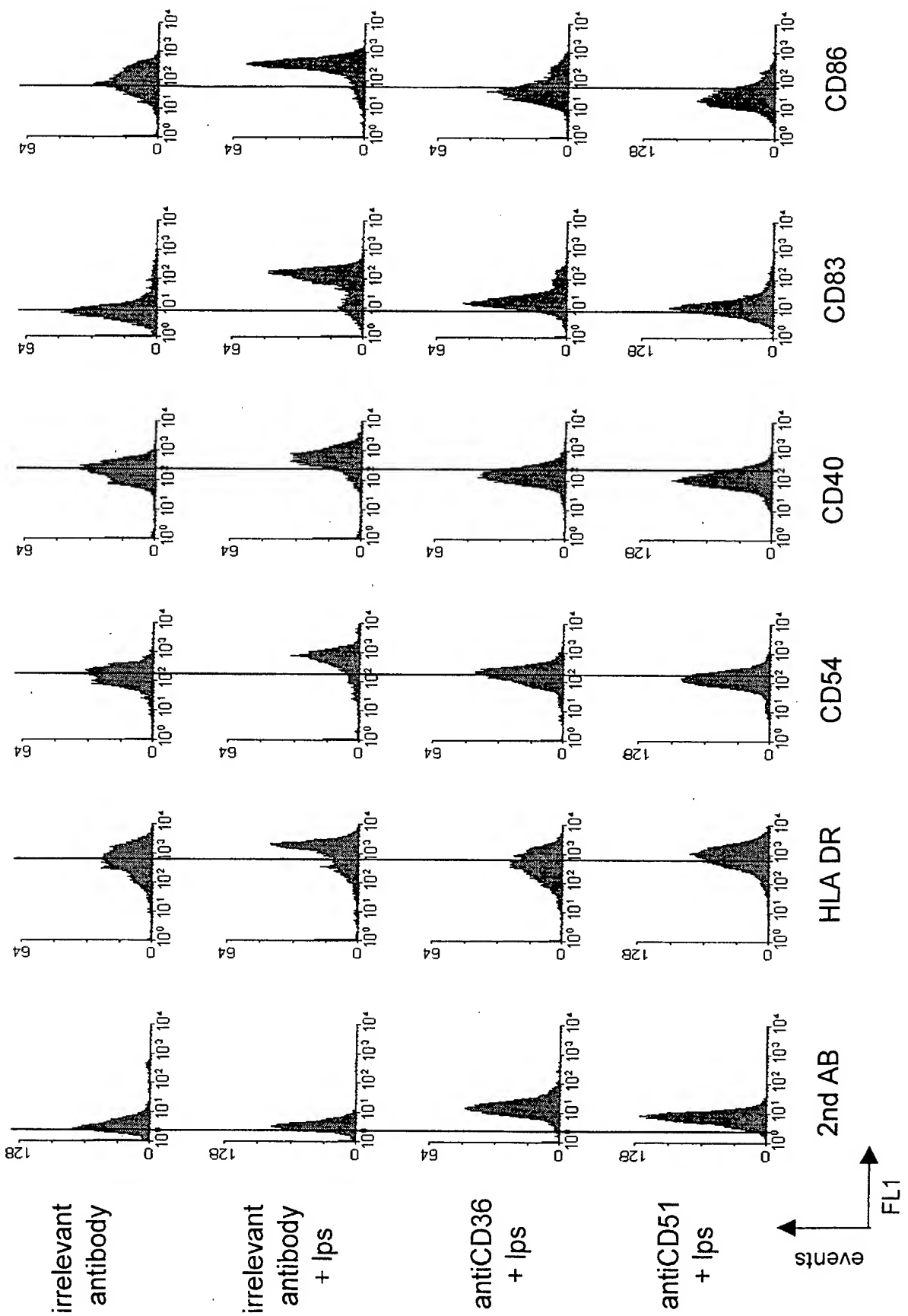

DC
DC lps
DC CD36 lps
DC CD51 lps
DC CD36/CD51 lps
DC HLA1 lps
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
DR
CD54
CD40
CD83
CD86

FIG. 8.


2nd AB
HLA DR
CD54
CD40
CD83
CD86
irrelevant antibody
irrelevant antibody + lps
antiCD36 + lps
antiCD51 + lps
events
FL1

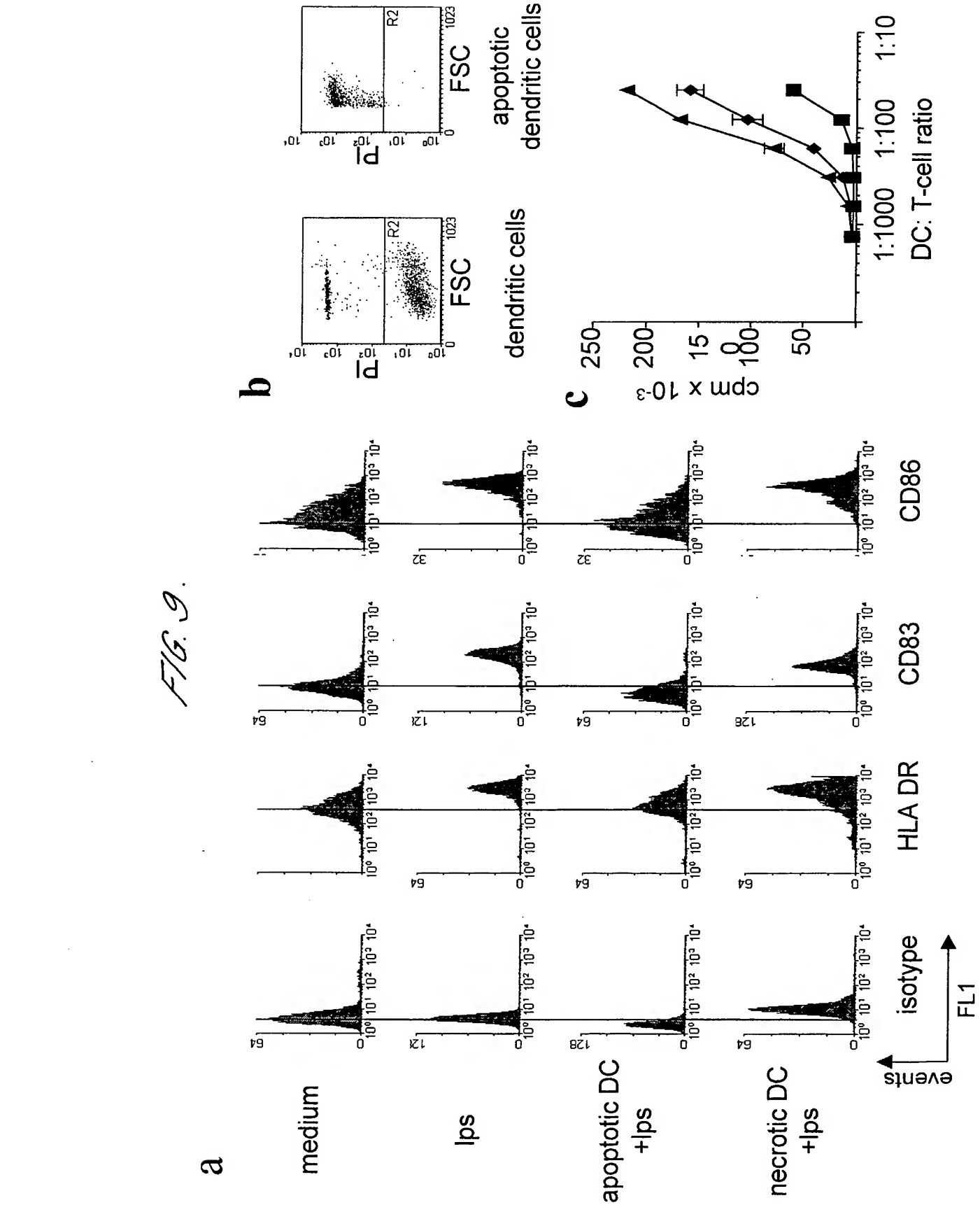

a
medium
lps
apoptotic DC +lps
necrotic DC +lps
isotype
HLA DR
CD83
CD86
events
FL1
b
PI
FSC
R2
dendritic cells
apoptotic dendritic cells
c
cpm x 10-3
250
200
150
100
50
1:1000
1:100
1:10
DC: T-cell ratio

FIG. 9.

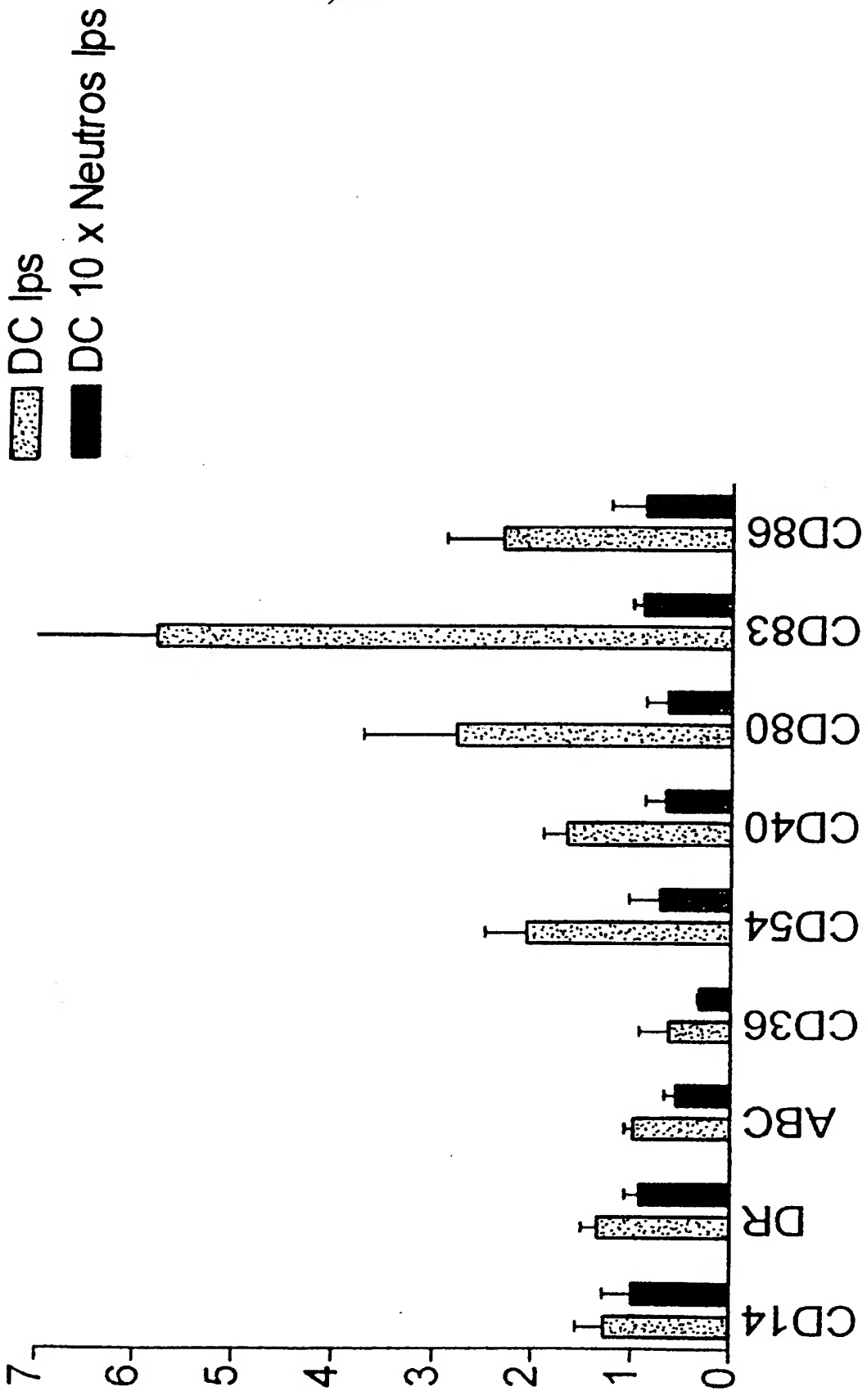
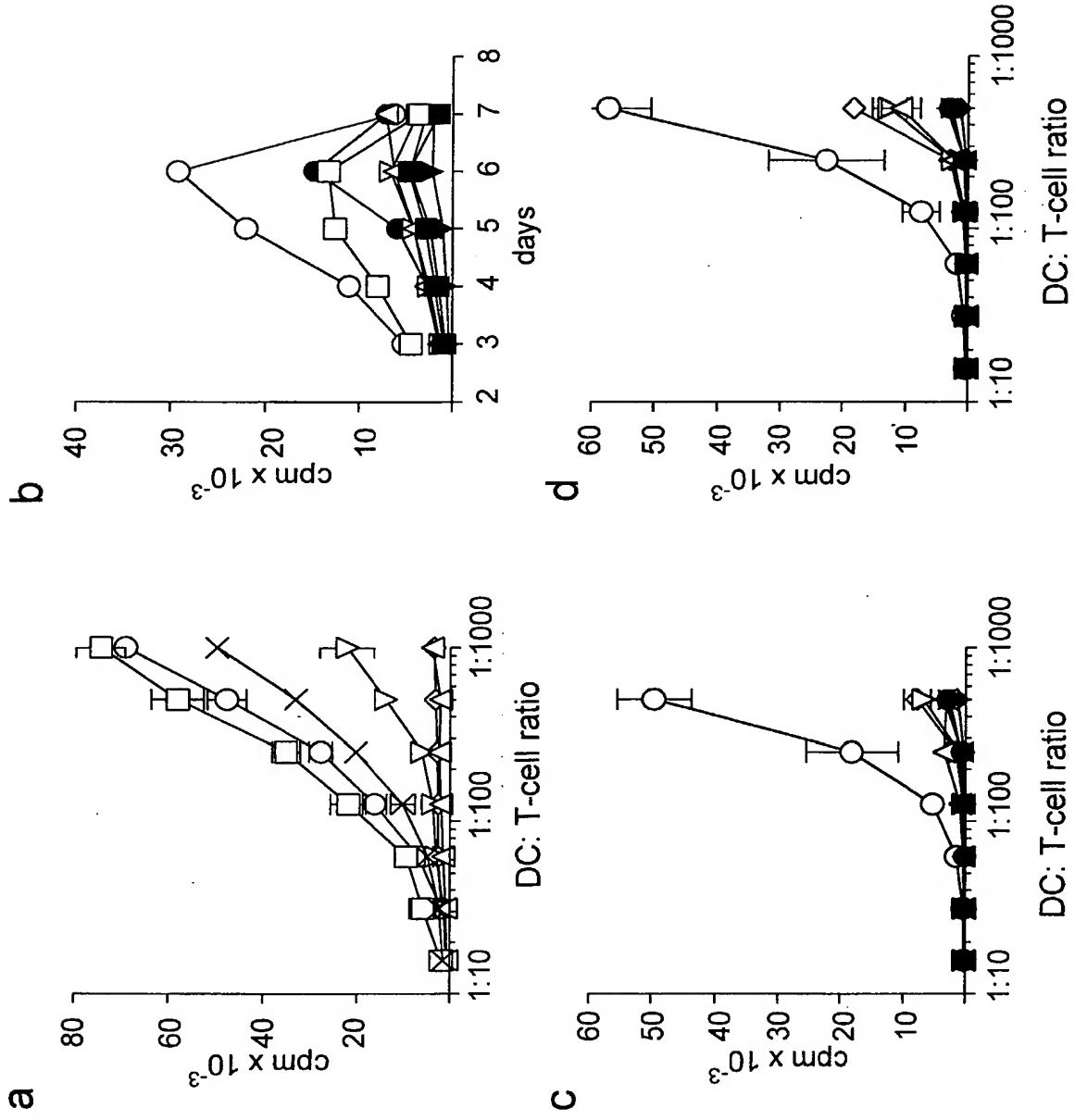

DC lps
DC 10 x Neutros lps
CD14
DR
ABC
CD36
CD54
CD40
CD80
CD83
CD86
0
1
2
3
4
5
6
7

FIG. 10.

FIG 11.


a
b
c
d
cpm x 10-3
DC: T-cell ratio
1:10
1:100
1:1000
days
2
3
4
5
6
7
8
10
20
30
40
50
60
80

12/13

FIG. 12.

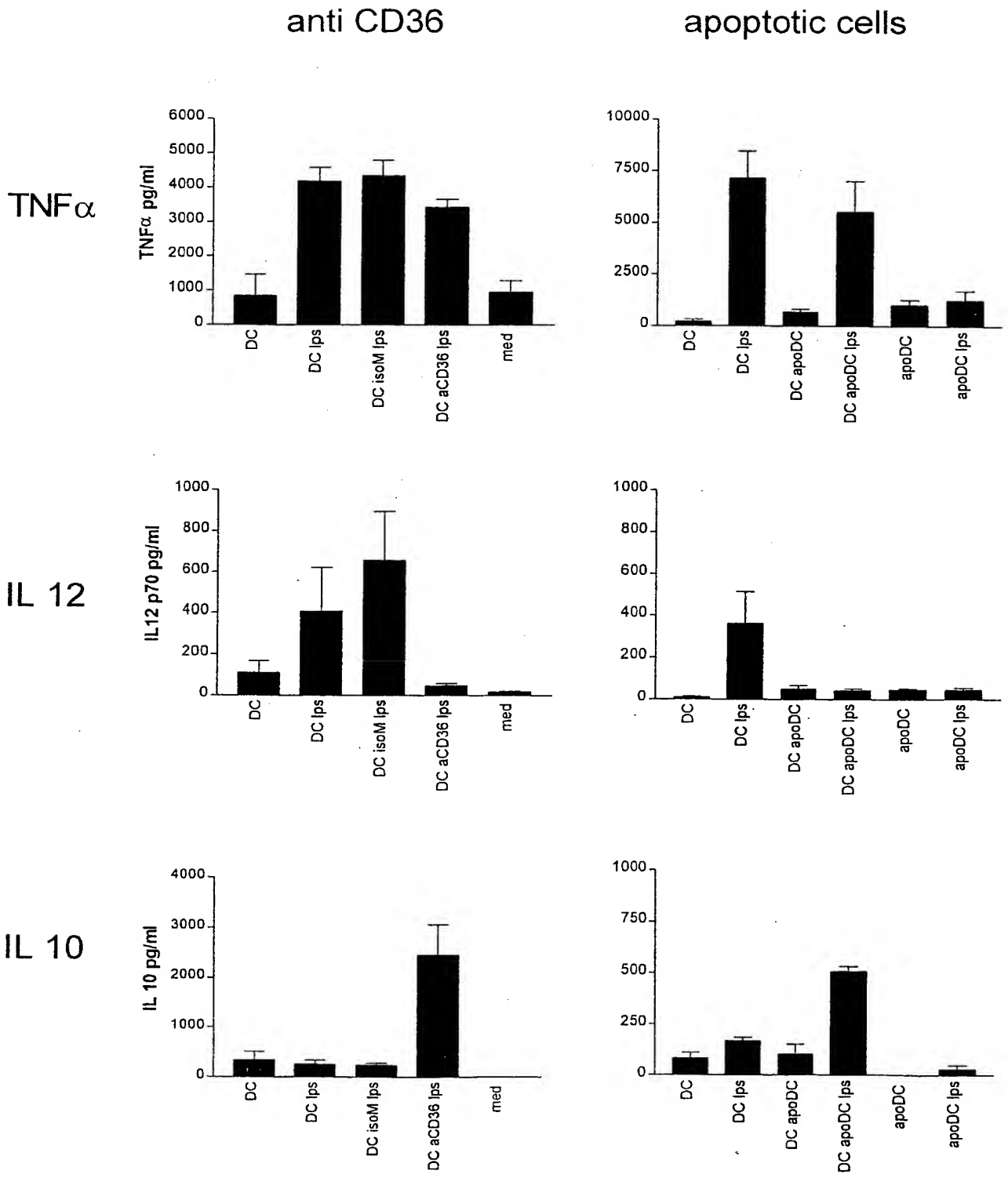

anti CD36
apoptotic cells
TNFα
IL 12
IL 10
TNFα pg/ml
IL12 p70 pg/ml
IL 10 pg/ml
DC
DC lps
DC isoM lps
DC aCD36 lps
med
DC apoDC
DC apoDC lps
apoDC
apoDC lps

FIG. 13.

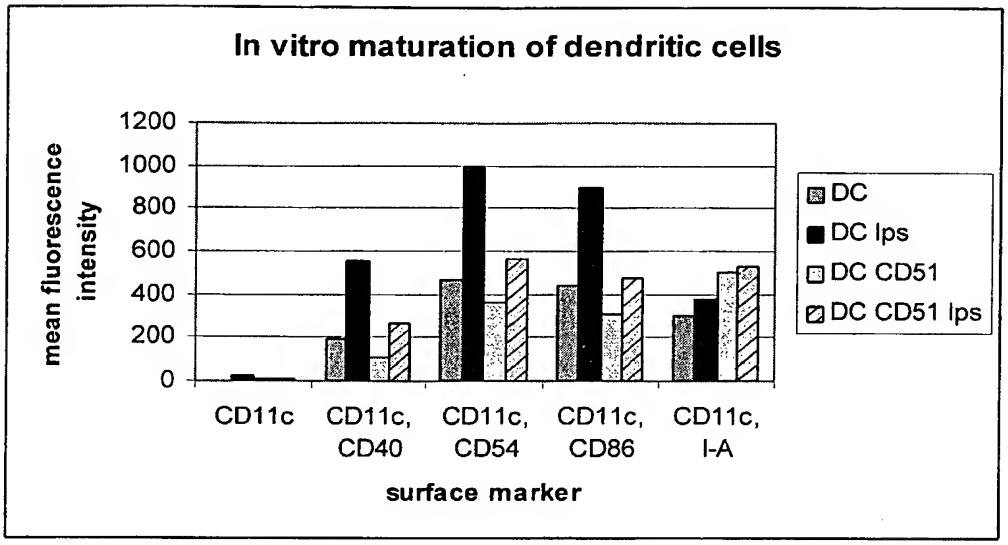
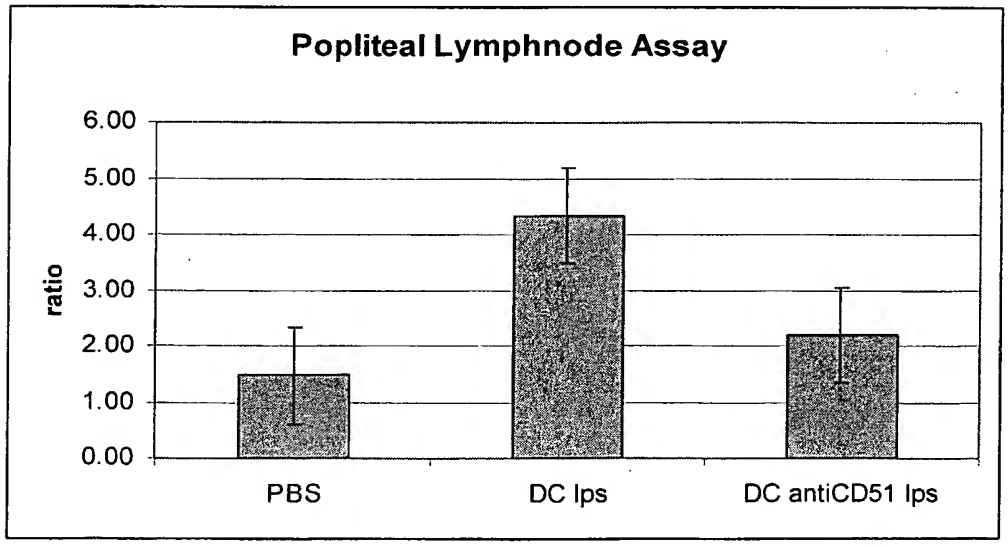

In vitro maturation of dendritic cells
mean fluorescence intensity
1200
1000
800
600
400
200
0
CD11c
CD11c, CD40
CD11c, CD54
CD11c, CD86
CD11c, I-A
surface marker
DC
DC Ips
DC CD51
DC CD51 Ips

FIG. 14.


Popliteal Lymphnode Assay
ratio
6.00
5.00
4.00
3.00
2.00
1.00
0.00
PBS
DC Ips
DC antiCD51 Ips